THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

Transition Metal-Mediated Selective Functionalizations of Bio-Derived Building Blocks

Iron- and palladium-based tools for building molecular complexity

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CHALMERS UNIVERSITY OF TECHNOLOGY

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Cover: Illustration of natural sources for some of the bio-derivable building blocks which have been utilized in this project: Wood as a source of phenols, chamomile as a source of azulenes and lingonberries as a source of benzoic acid. *Artist: Malin Bengtsson.*

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Abstract

In order to transition to a more sustainable chemical industry, it is necessary to replace the fossil starting materials that are largely used today with renewable ones. Starting materials available from abundant natural sources, or which can be efficiently produced via a biotransformation, are of high interest in this regard. The building blocks obtained from nature often differ from those derived from petroleum, both in composition and structure, and when the raw materials change, the chemistry we use needs to follow. Developing new ways to selectively modify these bio-derived starting materials is therefore of great importance. In this thesis, new methods for the selective functionalization of bio-derivable molecules are presented, with focus on materials available in bulk or which can be harnessed from a biotransformation. The goal is to produce new classes of chemicals which can be useful in various applications and to use the synthetic handles present in the starting materials to efficiently introduce a high degree of complexity.

The first part of this thesis concerns the iron-mediated nucleophilic addition to cationic iron carbonyl dienyl complexes. The scope of this reaction was expanded to include the selective *C*- or *O*-addition of phenols. Phenolic molecules are interesting as green building blocks, as they can be obtained in large quantities from lignin byproducts of the pulp and paper industry. In addition, azulenes were also shown to be competent nucleophiles in the addition reaction, where the azulene scope included guaiazulene, available from natural sources, and derivatives thereof. Azulenes have sparked a large recent interest due to their potential for applications in optoelectronic devices such as solar cells.

The second method investigated in this thesis is the palladium-catalyzed selective modification of a chiral building block obtained via a biotransformation of benzoic acid. Palladium-catalyzed Heck-type arylation showed an interesting synergy with the biocatalytically derived dihydroxylated cyclohexadienes, reacting with high selectivity and achieving a transfer of valuable steric information installed in the biotransformation to the newly formed C-C bond. This palladium-catalyzed transformation was also modelled using DFT calculations. Furthermore, if an *ortho*-iodo benzaldehyde is used as the aryl halide coupling partner, the arylation triggers a domino reaction, forming a chiral tetrahydrofluorenone. This domino reaction installs a high degree of complexity in a single synthetic step and represents an unprecedented acylation-terminated Heck-type reaction.

Keywords: *green chemistry, renewable resources, phenols, microbial arene oxidation, iron, metal carbonyl, Heck reaction, chirality transfer, domino reactions, azulenes, palladium*

List of publications

This thesis is based on the following publications:

I Selective Iron-Mediated C- and O-Addition of Phenolic Nucleophiles to a Cyclohexadiene Scaffold Using Renewable Precursors

P. Dunås, A. J. Paterson, G. Kociok-Köhn, S. E. Lewis, N. Kann.

ACS Sustain. Chem. Eng. **2019**, *7*, 7155–7162. https://doi.org/10.1021/acssuschemeng.9b00127.

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II Azulene Functionalization by Iron-Mediated Addition to a Cyclohexadiene Scaffold

P. Dunås, L. C. Murfin, O. J. Nilsson, N. Jame, S. E. Lewis, N. Kann.

J. Org. Chem. **2020**, *85*, 13453–13465. https://doi.org/10.1021/acs.joc.0c01412.

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III Palladium Catalyzed Stereoselective Arylation of Biocatalytically Derived Cyclic 1,3-Dienes: Chirality Transfer via a Heck-Type Mechanism

A. J. Paterson, P. Dunås, G. Kociok-Köhn, M. Rahm, P-O Norrby, S. E. Lewis, N. Kann.

Org. Lett. **2020**, *22*, 2464–2469. https://doi.org/10.1021/acs.orglett.0c00708.

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IV Palladium Catalyzed Stereoselective Domino Arylation-Acylation: An Entry to Chiral Hydrofluorenone Scaffolds

P. Dunås, A. J. Paterson, G. Kociok-Köhn, M. Rahm, S. E. Lewis, N. Kann.

Manuscript.

Contribution report

The author has made the following contributions to the papers:

Paper I — Main author. Active in the planning of the study, responsible for the major part of the experimental work and wrote part of the manuscript.

Paper II — Main author. Active in the planning of the study, performed or supervised all the experimental work except UV-vis/fluorescence spectroscopy and wrote the main part of the manuscript.

Paper III — Co-author (equal contribution). Active in the planning of the study, responsible for parts of the experimental work, responsible for the computational chemistry and helped in writing the manuscript.

Paper IV — Main author. Active in the planning of the study, responsible for all the experimental work except X-ray crystallography, and wrote the main part of the manuscript.

Abbreviations

BPDO	Biphenyl dioxygenase
BZDO	Benzoic acid dioxygenase
CAN	Ceric ammonium nitrate
cat	Catalytic
conc	Concentrated
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DFT	Density functional theory
DIEA	*N,N*-Diisopropylethylamine
DMF	*N,N*-Dimethylformamide
DMP	2,2-Dimethoxypropane
dppe	1,2-Bis(diphenylphosphino)ethane
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dppp	1,3-Bis(diphenylphosphino)propane
equiv	Equivalents
HOSA	Hydroxylamine-*O*-sulfonic acid
IR	Infrared
LiHMDS	Lithium bis(trimethylsilyl)amide
MAO	Microbial arene oxidation
2-Me-THF	2-Methyltetrahydrofuran
Ms	Methanesulfonate
MTBE	Methyl *tert*-butyl ether
NDO	Naphthalene dioxygenase
NMR	Nuclear magnetic resonance spectroscopy
NOE	Nuclear overhauser effect
Nu	Nucleophile
PES	Potential energy surface

Pd/C	Palladium on carbon
p-TsOH	*p*-Toluenesulfonic acid
rt	Room temperature
TBA	Tetrabutylammonium
TBDMS	*tert*-Butyldimethylsilyl
TDO	Toluene dioxygenase
TEA	Triethylamine
Tf	Trifluoromethanesulfonate
TFA	Trifluoroacetic acid
THF	Tetrahydrofurane
TMA	Tetramethylammonium
TMANO	Trimethylamine *N*-oxide
TMS	Trimethylsilyl
Ts	*p*-Toluenesulfonate
TS	Transition state
UV	Ultraviolet

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1. Introduction

The advances made in the field of chemistry have been revolutionary to our society. Chemistry and chemical products are an integral part of our lives today. Chemistry is used to produce food, materials, medicines and almost all the products we use every day. Three examples of chemicals which have had a large impact on our society are shown in Figure 1. Sodium stearate is a major component in bar soap, and production of soap-like products dates back to at least the third millennium BC.[1] Soap has had a large impact in combating infectious diseases, and in the recent outbreak of COVID-19, soap has been shown to be the most effective method for hand sanitization.[2,3] Polyethylene is the most common plastic in use today.[4] While this plastic material is an integral part of our everyday lives, its low biodegradability and use in disposable products and packaging leads to problems with littering and accumulation of plastic in nature. Lastly, penicillin, discovered by Sir Alexander Fleming in 1928,[5] is one of the medical discoveries which has had the most impact, initiating the development of modern antibiotics.[6,7]

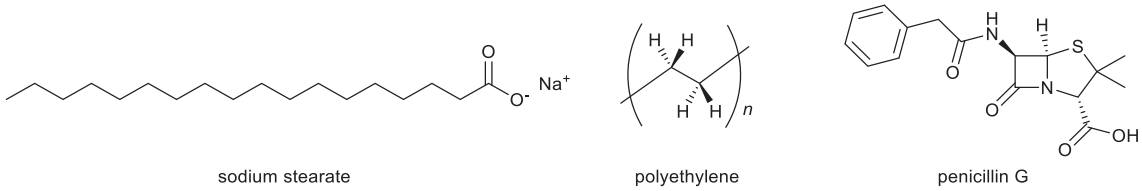


Figure 1 Structures of sodium stearate, polyethylene and penicillin G.

1.1 Chemistry today and in the future

In the time since the industrial revolution, amazing progress has been made in science and technology, including advancements in the chemical sciences. However, for a long time these advances were made with little consideration for the environment, and the long-term sustainability of the planet. By the second half of the 20th century, the effects of increasing pollution could be seen and the environmental movements were growing, wanting to draw attention to the connection between economic growth and environmental degradation.[8,9] This conflict eventually led the United Nations to establish the Bruntland commission, to propose long term environmental strategies to achieve a sustainable development. The report produced by the commission in 1987 defines sustainable development as '*development that meets the needs of the present without compromising the ability of future generations to meet their own needs'*.[10]

Today, the majority of chemicals are based on non-renewable feedstock,[11] which contributes to the depletion of natural resources. In addition, the use of fossil starting materials adds to the release of greenhouse gases responsible for global warming. In order to reach a sustainable production of chemicals, a change to renewable starting materials is necessary. This will require new chemistry, adapted to starting materials available from nature rather than petroleum-based feedstock, and the chemical transformations used to refine these starting materials into valuable chemicals also need to be sustainable. Chemical processes which use hazardous reagents, have a high energy demand or create large amounts of waste, should be avoided. Ideally these processes should be optimized to reduce their environmental impact. This field of study is known as green chemistry.

1.1.1 Green chemistry

The concept of green chemistry emerged around the beginning of the 1990s, and represented a change in focus from end-of-pipe control to pollution prevention, with the intention of making chemistry "benign by design".[12] In 1998, Paul Anastas and John Warner published a green chemistry handbook which presented the twelve principles of green chemistry, a set of guidelines to assist in the development of green chemical processes.[13] These principles are:

1. Waste prevention
2. Atom economy
3. Less hazardous chemical syntheses
4. Designing safer chemicals
5. Safer solvents and auxiliaries
6. Design for energy efficiency
7. Use of renewable feedstocks
8. Reduce derivatization
9. Catalysis
10. Design for degradation
11. Real-time analysis for pollution prevention
12. Inherently safer chemistry for accident prevention

The twelve principles can be used as guidelines in the development of more efficient, safer chemistry that produces less waste and consumes less resources. A brief description of some of the key points relevant to this thesis follows.

Typically, solvent comprises 80 – 90% of the mass put into a fine chemical or pharmaceutical batch chemical operation, and the solvents are often dominant in the overall toxicity profile of a process.[14] The choice of solvent plays a large role for the overall sustainability of a reaction, and the selection of solvent is therefore an important factor in designing a green chemical transformation. In addition to how sustainably the solvent itself is sourced, many factors affect the greenness of a solvent, such as the toxicity, flammability and the energy demands of separating the products from the crude reaction mixture. To assess the sustainability of a solvent, a number of metrics and solvent selection guides have been developed.[15]

Atom economy introduced by Barry Trost is an important metric used in green chemistry. It is defined as the molecular weight of the desired product divided by the molecular weight of all reactants *100%.[16] The atom economy assumes full conversion to the desired products, and does not factor in the use of solvents or additives. Other metrics that takes this into account exist.[17] One such metric is the environmental factor, or E-factor, defined by Roger Sheldon as the total mass of waste produced per unit mass of product.[18,19] While the atom economy describes the efficiency of a reaction itself, the E-factor is a metric for the efficiency of a process.

Catalysis increases the rate of a reaction through the addition of a catalyst. The catalyst is both a reactant and a product of the reaction and is not consumed.[20] A catalyst can be used to alter the selectivity of a reaction by increasing the rate of one reaction over another. It can open up the possibility to perform reactions which would otherwise be practically impossible by providing a

drastic increase in reaction rate and it can make it feasible to perform chemical reactions under much milder conditions. The fact that the catalyst is not consumed in the reaction makes it superior to stoichiometric reagents for performing reactions with a high atom economy, this can also make it possible to recover the catalyst unchanged after the reaction.

1.1.2 Utilizing natural materials and exploiting their inherent complexity

A sustainable chemical production should be based on renewable starting materials. However, many of these have a different composition and a more complex structure compared to the classic petroleum based starting materials. In order to transition to a chemical industry based on biomass, new chemical methods need to be developed. If most chemicals are to be produced from renewable feedstock however, large amounts of biomass will be needed, and for the production of high-volume chemicals the focus must be on resources available in bulk quantities. Lignocellulosic biomass is the most abundant renewable biomass on earth and is a promising carbon source for building a renewable platform for chemical production in the future.[21,22] Softwood biomass such as spruce typically contains around 45% cellulose, which is extensively used by the pulp and paper industry, along with 25% hemicellulose and 25% lignin.[22] Today, the lignin is mostly burned for energy on site, but extensive research on how to better utilize this waste stream is in progress. One alternative is depolymerization of the lignin to provide a range of small oxygenated aromatic molecules, some examples are shown in Figure 2.[23,24] The development of new chemistry that can utilize these renewable aromatic building blocks for the production of fine chemicals is an important step towards a sustainable chemical industry.

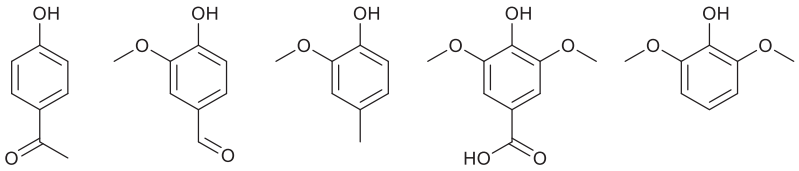
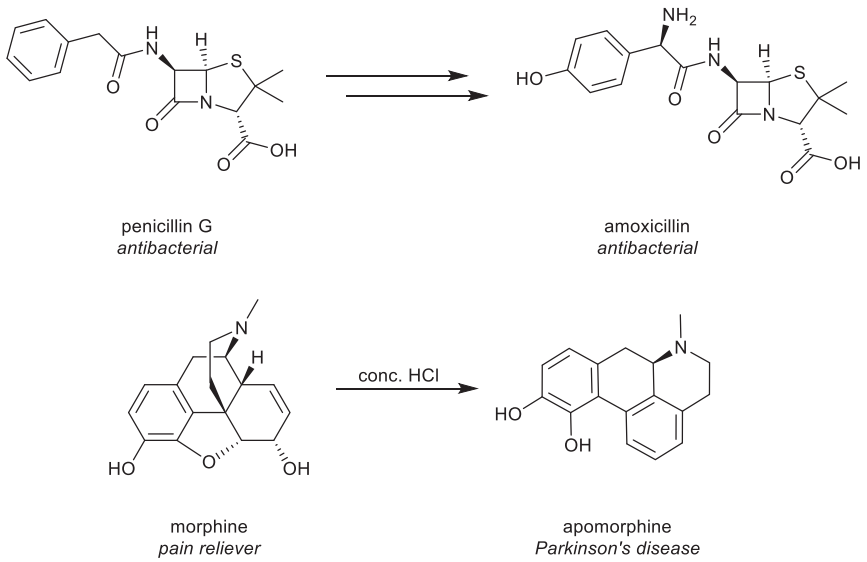


Figure 2 Examples of phenolic monomers which could potentially be obtained from lignin.[23,24]

Synthetic modifications of more scarce natural products are also of great importance in modern chemistry. These complex natural starting materials are valuable in the production of fine chemicals, and for medicinal chemistry in particular.[25] Aspirin, commercialized in 1899 was the first synthetic analog of a natural product to be used as a medicine,[26] and the discovery of penicillin in 1928 led to a large breakthrough in the synthesis of medicines from naturally derived substances.[25] Natural product derivatives are a major source for new drug discoveries even today, comprising 27.5% of all new approved small molecule drugs in the years 1981 to 2019.[27]

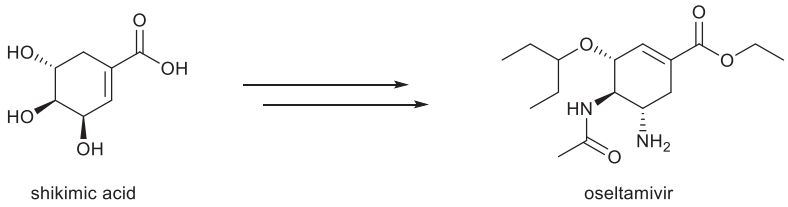
In medicine, chemical synthesis based on natural products has mainly focused on improving the drug-like features already present in the natural product. One such example is the synthesis of amoxicillin from penicillin G, where both compounds are antibiotics of the same class (penicillins), but the semi-synthetic amoxicillin is effective against a wider spectrum of bacteria (Scheme 1).[28] Another approach is to use natural products as starting materials, utilizing the high complexity present in nature to make novel substances with new properties that are not present in the original molecule.[29] One such substance is apomorphine, produced by treating morphine with concentrated hydrochloric acid.[30] In the process, morphine loses its affinity for opioid receptors,

but instead the produced apomorphine possesses significant dopamine receptor antagonist activity. This results in a novel medicine, and apomorphine is marketed for treatment of both Parkinson's disease and erectile dysfunction.[29]



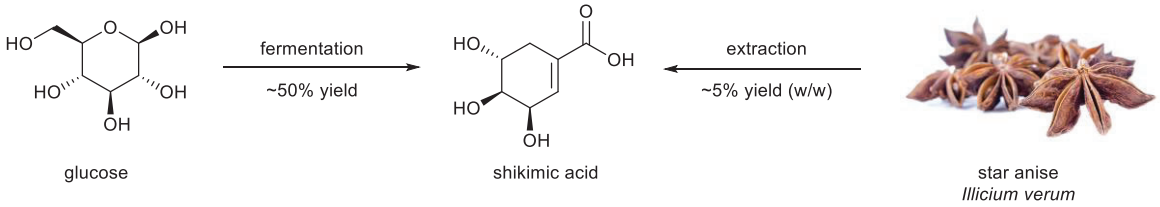
Scheme 1 Different strategies for developing semisynthetic drugs.

The need to isolate starting materials from natural sources, where they are often found in low concentrations, can have some drawbacks, however. Oseltamivir is an antiviral drug, synthesized from the natural product shikimic acid (Scheme 2).[31]



Scheme 2 Shikimic acid, used as a starting material for the commercial synthesis of the antiviral drug oseltamivir.

Shikimic acid in turn has star anise as its major commercial source, where it can be extracted from the dried fruits in a yield of around 5% (Scheme 3).[32] With the outbreak of the swine flu pandemic in 2009, many countries started stockpiling oseltamivir, and a shortage of supply in shikimic acid followed, with prices increasing tenfold.[33] In addition, China is responsible for 80-90% of the global star anise production, with a majority produced in the Yunnan and Guanxi provinces, making the supply vulnerable to environmental factors such as draught and floods.[33] Being a natural product, biosynthetic pathways to access shikimic acid exist which could also be identified in bacteria. This can be utilized in fermentation processes where bacteria such as recombinant *E. coli* strains can produce shikimic acid from glucose in up to 50% yield.[32] Today, a significant part of the produced shikimic acid is of microbial origin.[31,33]



Scheme 3 Major commercial sources of shikimic acid, fermentation and extraction from plant sources.

Development of new methods for the selective modification of molecules derived from biological sources, which can utilize and expand upon the complexity present in the natural products, is of great interest. Using materials derived from abundant natural sources, as well as the ability to produce these valuable starting materials using biotransformations rather than extraction from biomass, can be important strategies to secure the future supply of complex chemicals. Therefore, the selective functionalization of molecules available from these sources is of great interest.

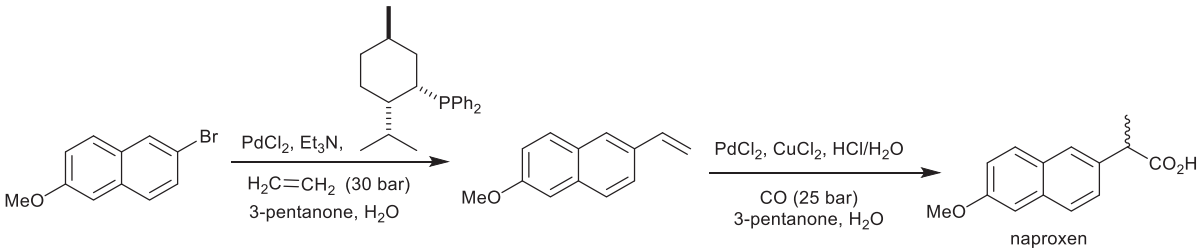
1.2 Transition metal-mediated reactions

The coordination of a metal to an organic molecule can drastically alter its reactivity. Early examples of organometallic reagents such as organomagnesium and organolithium compounds have had a revolutionary impact in organic chemistry by providing stabilized, but still reactive, carbanions which can serve as powerful nucleophiles or strong bases.[34] The later development of organotransition metal chemistry has had a different type of impact, here the coordination to the metal can open up totally new ways of breaking or forming bonds. Often these metals can be applied in catalytic amounts, and this has allowed the development of many new reactions and synthetic pathways.[35]

1.2.1 Noble metal catalysis

Several noble metals such as ruthenium, rhodium, iridium and palladium have been used extensively in catalytic reactions where they show a great versatility in mediating selective transformations.[36,37] Palladium in particular has found many applications thanks to its capability to catalyze a wide range of useful carbon-carbon bond formation reactions.[38]

Although these precious metals are expensive, they can provide access to reactions and compounds which would otherwise be inaccessible using conventional synthetic methods. Often low catalytic loadings of these precious metals are required, in many cases making them the most economic option. For example, the industrial synthesis of the anti-inflammatory drug naproxen by Albemarle uses a palladium-catalyzed Heck reaction for one of the key couplings. With a catalytic loading of less than 0.05% the reaction completes within a few hours (Scheme 4).[39]



Scheme 4 Synthesis of naproxen via a Heck reaction followed by hydroxycarbonylation.[39]

Although responsible use of rare metals might be a good option in some cases, they can be problematic. In addition to their high price, these precious metals show a high environmental burden of extraction, if compared on a per kilogram basis.[40] Many transition metals risk depletion if the current use continues (Figure 3). Several metals also have their main known reserves in conflict zones or areas where human rights are not respected, increasing the risk for an unstable supply, as well as raising concerns for the conditions in which they are extracted.[41] These issues have led to efforts to replace expensive and problematic metals with more sustainable alternatives.

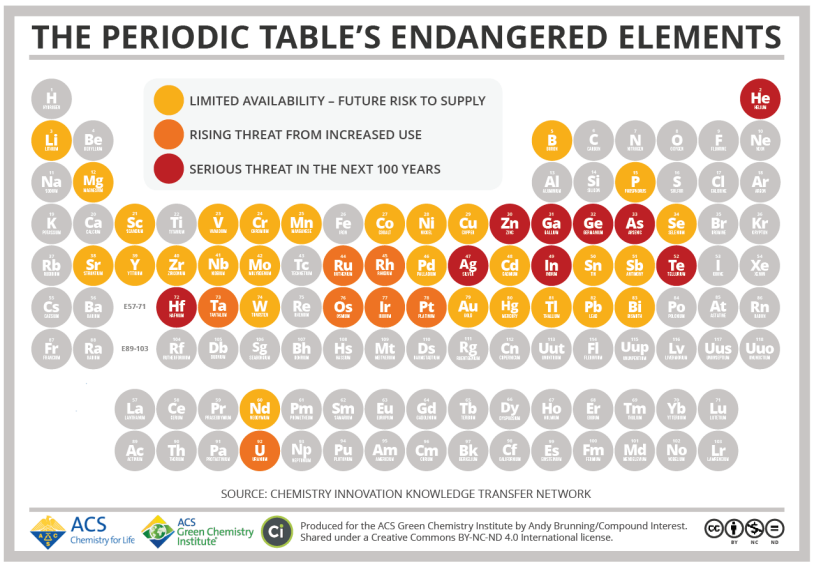
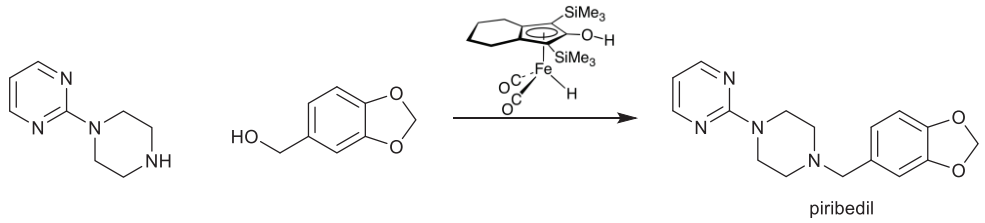


Figure 3 Elements facing risk of depletion. Picture produced for the ACS Green Chemistry Institute by Andy Brunning/Compound Interest. Shared under a Creative Commons BY-NC-ND 4.0 International license.

1.2.2 Iron-mediated reactions

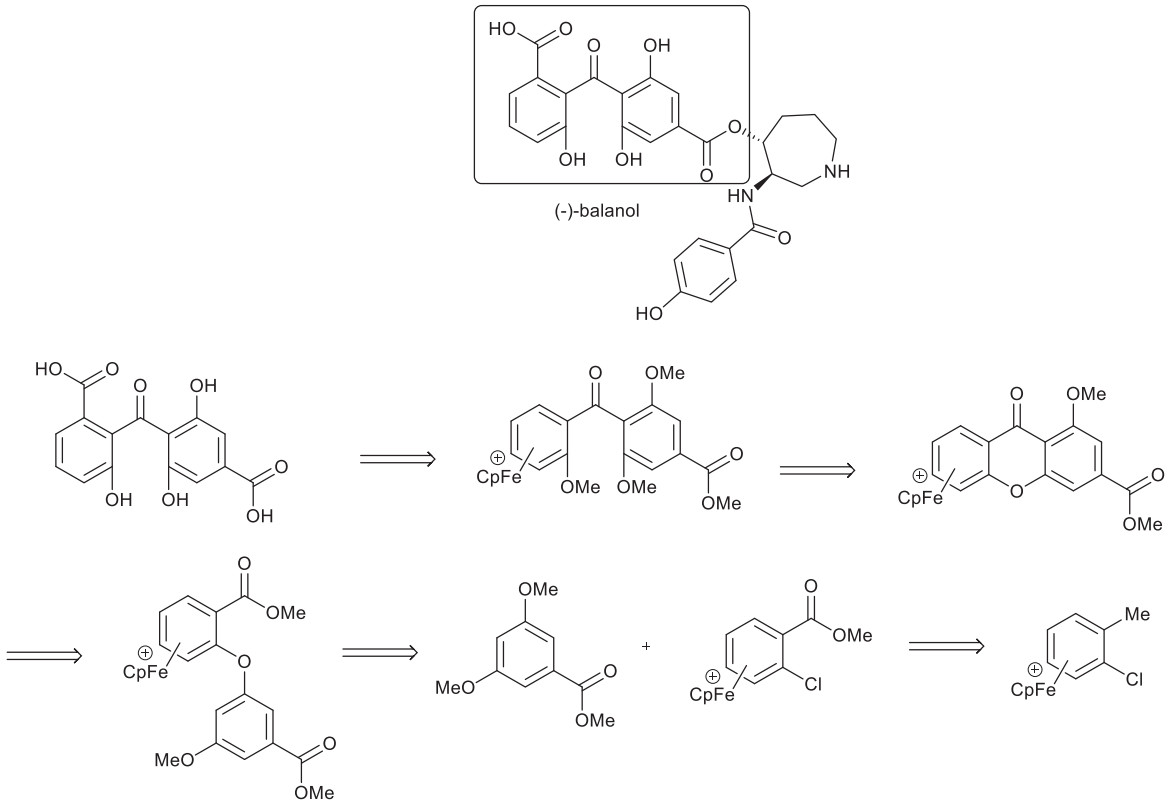
Iron is one of the most sustainable transition metals. It is cheap, relatively non-toxic[42] and abundant, and the known deposits are widespread.[43] In addition, the production of iron has one of the lowest environmental impacts per unit mass, in terms of both global warming potential and more local impact, such as terrestrial acidification.[40] Despite this, the use of organoiron chemistry has been somewhat restricted compared to other metals that are mainly used in catalytic processes such as palladium.[44] As opposed to many other organometallic complexes, organoiron complexes are often stable to air and moisture and thus easy to handle. This makes iron an excellent candidate for use as a green reagent in organic synthesis.

In the last decades, iron catalysis has become a highly researched area. Through development of specialized ligands and smart design of catalytic systems, many of the transformations previously restricted to noble metal catalysts can now be performed using iron.[45,46] As an example, the recent developments in iron-based catalysts has made it possible to perform hydrogen autotransfer reactions using iron catalysis,[47,48] where these reactions were previously restricted to noble metal catalysts.[49] Scheme 5 shows the synthesis of the pharmaceutical piribedil by hydrogen autotransfer, catalyzed by an iron complex formed in situ, as demonstrated by Feringa and Barta.[47]



Scheme 5 Synthesis of the dopamine antagonist piribedil by iron-catalyzed hydrogen autotransfer.[47]

The sustainability, low price and low toxicity of iron also makes it a good candidate for use as a stoichiometric reagent, especially if the iron moiety can be retained and exploited in a series of transformations. An example of the utility of these types of iron-mediated methods is a synthesis of the sterically congested benzophenone moiety of the protein kinase C inhibitor balanol, reported by Andersson, where all the key steps rely on iron-mediated reactions (Scheme 6).[50]



Scheme 6 Retrosynthetic analysis of balanol based on iron-mediated transformations.[50]

1.3 Biocatalysis

The use of living systems, or enzymes produced by living systems to catalyze chemical transformations is known as biocatalysis.[51] In the form of fermentation, biocatalysts performs some of the oldest forms of chemical transformations known by man and fermentation has been used since Neolithic times in order to preserve food and produce alcoholic beverages.[52] For a long time, however, it was believed that the substances and processes in living matter were fundamentally different from those in non-living processes and did not follow the known laws of chemistry and physics, a theory known as vitalism. A first step towards refuting this belief was taken in 1828 when Friedrich Wöhler showed that urea, a substance until then known only from biological origin, could be synthesized in a laboratory from inorganic precursors.[53,54] Louis Pasteur showed that microorganisms were responsible for fermentation processes, and he also argued that life was necessary to catalyze these processes.[55,56] This was disproved in 1872 by Maria Manaseina, who demonstrated that cell-free extracts of yeast could ferment sugar to alcohol.[57,58] These findings were confirmed by Eduard Buchner in the late nineteenth century, who despite being aware of Manaseina's discoveries, failed to reference them.[59] Buchner hypothesized that the fermentation was effected by proteins (enzymes) produced by the yeast cells.[60]

After these initial developments, a growing interest was seen in the area of biocatalysis, leading to a number of patents and industrial processes.[51] Today, biocatalysis has found many applications towards the production of fine chemicals. As an example, the enzymatic resolution of amines to produce enantiomerically pure products is conducted on a multithousand ton per year scale in the BASF ChiPros process (Scheme 7).[61,62]

Scheme 7 Lipase-catalyzed resolution of chiral amines.[62]

The use of biocatalysis has even reached the production of bulk chemicals. Acrylamide is produced from acrylonitrile using the enzyme nitrile hydratase, expressed by *Rhodococcus rhodochrous,* on a scale exceeding 650 000 tons annually.[63] Directed evolution of enzymes has opened up a new way to develop improved biocatalysts by mimicking the process of natural selection.[64] This has been used to increase the thermal stability of enzymes, make them more tolerant to organic solvents or even to achieve chemical transformations unknown in natural systems.[65,66]

Biocatalysis has also attracted attention as a green synthetic method.[67] Enzymes are capable of performing many reactions with excellent selectivity without the use of precious metals, under mild conditions at close to ambient temperatures, without producing toxic waste. Furthermore, the reactions are often performed in water and the enzymes themselves are renewable.[62]

1.4 Computational chemistry

Computational chemistry is a branch of theoretical chemistry, where the aid of computer simulations is used in order to solve chemical problems. Computational chemistry can be used to

calculate a wide range of properties such as structure, energy, vibrational frequencies, charge density distribution or NMR coupling constants.[68] Applications to organic synthesis include mapping out reaction paths by modelling transition states and calculating energy barriers in order to help elucidate or explain a reaction mechanism. Computational chemists have several different methods at their disposal to help answer these types of questions.[69]

1.4.1 Methods

Molecular mechanics is based on empirical information of normal bond lengths and angles and how much energy is required to stretch and bend these bonds. Based on this knowledge, the energy of a given molecular conformation can be estimated.[69] Molecular mechanics requires relatively small computational power and can therefore be used as a fast method to obtain a rough estimation of the structure or relative energy of a compound.

Ab initio calculations attempt to calculate molecular properties from the basic principles of quantum mechanics, by solving the Schrödinger equation to calculate the wave function, describing the electrons in a given molecular geometry.[70] The Schrödinger equation cannot be solved analytically for molecules with more than one electron, so some approximations are used. The less serious these approximations are, the higher level the ab initio calculation is said to be. Ab initio calculations are quite demanding and to be able to use these types of calculations within reasonable time on anything else than a very small molecule, powerful computers are needed.[69]

Semiempirical methods are based on solving the Schrödinger equation, as in the ab initio method. In the process, more approximations are made and instead of performing the demanding calculations, semiempirical methods use a library of experimental or theoretical parameters which are plugged into the calculation.[71] This process saves a lot of time compared to ab initio methods, but with a risk that the used parameters are not a good fit for the calculation in question.

Density functional theory (DFT) is a method that, instead of calculating the wave function, attempts to calculate the electron density distribution directly by solving a number of Schrödinger-like equations.[69] Various molecular properties can then be determined, based on the Hohenberg-Kohn theorems stating that the ground-state properties of a molecule can be determined by its electron density function.[72] DFT calculations are usually faster than ab initio, and this is today the most popular method in computational chemistry.[73]

1.5 Azulenes

Azulene (**1**) is an aromatic hydrocarbon, isomeric with naphthalene but consisting of two fused seven- and five-membered rings. The π-electrons of azulene are polarized towards the five-membered ring, achieving Hückel aromaticity while giving the azulene some character of a cyclopentadienyl anion fused to a tropylium cation (Figure 4).[74] As a result, azulene has an unusually high dipole moment for a hydrocarbon, with a value of 1.08 D,[75] as well as significant nucleophilicity at the 1- and 3-positions.[76]

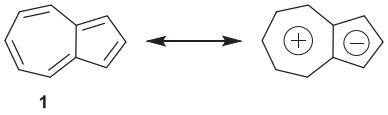


Figure 4 Azulene and the resonance responsible for its dipole character.

The unusual electronic properties of azulene gives it several interesting optical attributes. Most azulenes have vibrant colors, azulene itself being deep blue.[77,78] Azulene is also fluorescent, with an unusual anti-Kasha's rule emission, i.e. fluorescence from the second excited state, rather than the first.[79]

Azulenes were first discovered as colorful distillates from various essential oils, such as wormwood and chamomile, or from oxidation products of various sesquiterpenes.[80] One of these natural azulenes, guaiazulene (**2**, Figure 5), is a commercial product, used as an additive in cosmetics.[81]

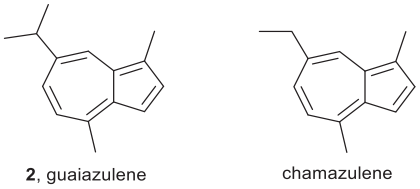
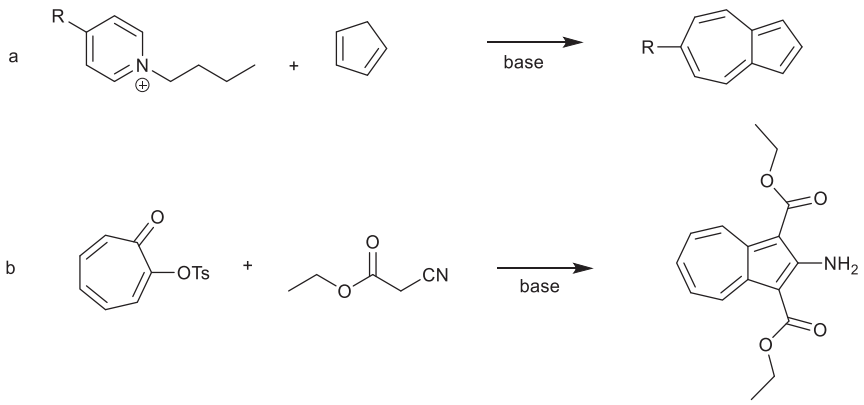


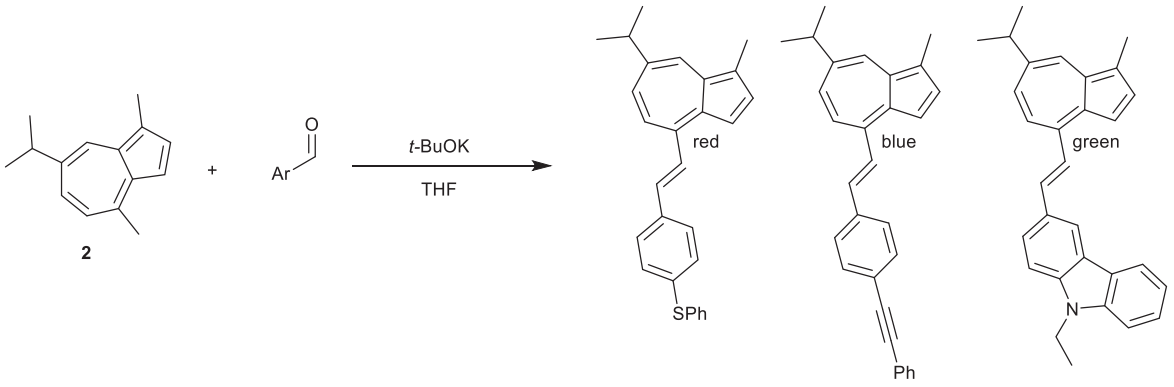
Figure 5 Guaiazulene and chamazulene, two azulenes found in the essential oil of chamomile.[82]

In addition to the naturally occurring azulenes, several synthetic approaches to access azulenes have been developed, such as the Ziegler-Hafner[83] and Nozoe[84] methods, presented in Scheme 8. Further examples are a ring expansion reported by Danheiser, starting from β′-bromo-α-diazo ketones,[85] and also Hawker's method, based on a cycloaddition reaction between thiophene-*S,S*-dioxides and fulvenes.[86]



Scheme 8 Synthesis of azulenes by a: modification of the Ziegler-Hafner method,[83,87] *b: the Nozoe method.*[84]

Interestingly, the optical properties of azulenes can be tuned by functionalization of the azulene skeleton. This was elegantly demonstrated by Belfield, who created a wide range of different colored chromophores by condensation reactions of the 4-methyl group of guaiazulene with different aromatic aldehydes (Scheme 9).[88]



Scheme 9 Examples of chromophores synthesized by condensation reactions between guaiazulene and aromatic aldehydes.[88]

The changes in optical properties upon modification of the azulene skeleton has also been used in the development of several azulene-based sensors, where exposure to a specific analyte induces a visible or otherwise measurable change in color and/or fluorescence.[89–93] An example of an azulene-based fluoride sensor developed by Lewis can be seen in Figure 6.[94] Upon exposure to fluoride ions, a color change from blue to yellow visible to the naked eye is induced in the azulene-boronic ester.

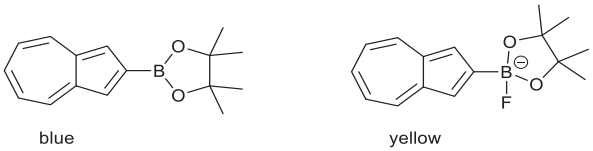


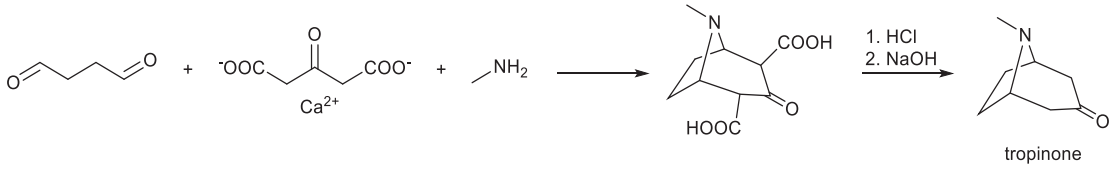
Figure 6 An azulene-based colorimetric sensor for fluoride ions.[94]

Azulene has also sparked an interest in various optoelectronic applications such as organic electronics and solar cells.[95] In addition to the previously mentioned anti-ulcer medication, azulene derivatives have also been promising for other medical applications such as antidiabetic[96] and anticancer[97] agents.

1.6 Domino reactions

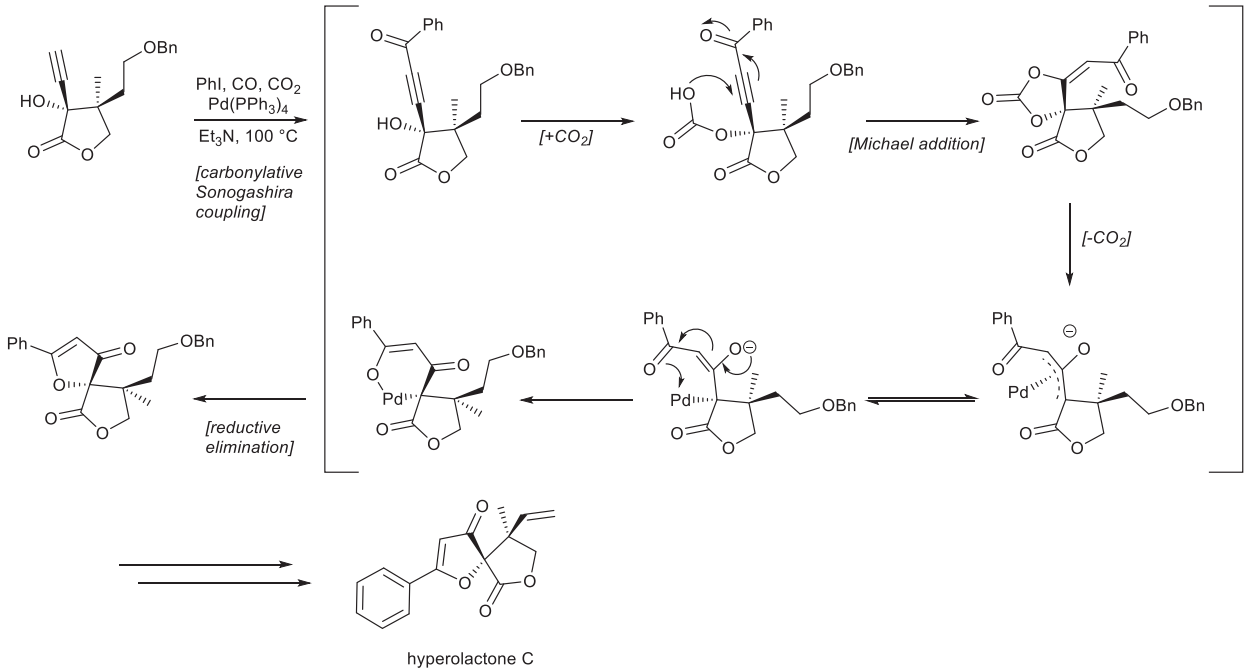
A domino reaction is a process where two or more consecutive reactions take place, and subsequent transformations can occur as a consequence of the previous reaction in the sequence.[98] Furthermore, the reaction sequence should proceed without change in reaction conditions between the steps, differentiating a domino reaction from a one-pot reaction, where addition of new material or other changes in the reaction conditions (but not isolation of intermediates) are allowed.

Domino reactions have proven to be powerful tools in natural product synthesis, where many reaction steps are often needed to reach the target structure.[99] The first reported domino reaction for the synthesis of a natural product is commonly ascribed to Robinson's one-pot synthesis of the alkaloid tropinone in 1917,[100] where the first step consists of two consecutive Mannich reactions (Scheme 10).



Scheme 10 Robinson's one-pot synthesis of tropinone.[100]

Domino reactions have since then emerged as an excellent way to introduce high degree of structural complexity using simple reaction conditions.[101] One elegant example is the palladium-catalyzed domino reaction used by Nicolaou in the synthesis of hyperolactone C (Scheme 11).[102]



Scheme 11 Palladium-catalyzed domino reaction used for synthesis of the core skeleton of hyperolactone C.[102]

In classical stepwise organic synthesis, purification and isolation of intermediates is often one of the most time consuming and waste creating processes. In addition, each consecutive reaction requires more energy, solvents and reagents. Utilizing domino reactions, forming multiple bonds in a single step is an important strategy to minimize waste formation and energy consumption, as well as the amount of labor required.[103] With their high efficiency, domino reactions are therefore an important tool within green chemistry.[99,104,105] Looking at the 12 principles of green chemistry, domino reactions are inherently able to provide significant improvements when it comes to (1) waste prevention, (2) atom economy, (6) design for energy efficiency, and (8) the possibility to reduce derivatization. In addition, many domino reactions rely on the use of catalysis (9).

2. Theory

2.1 Iron carbonyl chemistry

Iron carbonyl chemistry started with the discovery of pentacarbonyliron (Figure 7) in 1891, independently by Mond[106] and Berthelot.[107] The compound was synthesized by exposing finely divided iron to carbon monoxide gas, obtaining a pale yellow viscous liquid.[108] Aside from the pentacarbonyl complex, iron can form two more stable homoleptic complexes with carbon monoxide, nonacarbonyldiiron and docecacarbonyltriiron (Figure 7). Nonacarbonyldiiron can be prepared photolytically from pentacarbonyliron, and dodecacarbonyltriiron is obtained by thermal decomposition of nonacarbonyldiiron.[109] Iron pentacarbonyl and nonacarbonyldiiron are the most commonly used precursors to organic iron carbonyl complexes, and they are both commercially available. There are some safety concerns when working with iron carbonyls, however. As with other metal carbonyls, they have the potential to release toxic carbon monoxide, a property which has also found medical applications.[110] Special care needs to be taken when handling pentacarbonyliron, as it is volatile, highly flammable, and toxic.[111,112] It is, however considerably less toxic than its infamous nickel carbonyl analogue.[113] Nonacarbonyldiiron is a non-volatile solid and therefore easier to handle.

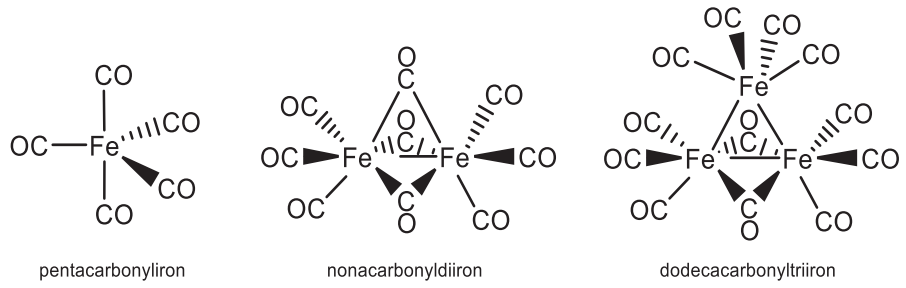
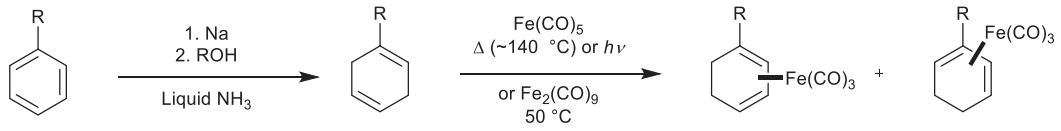


Figure 7 The three known stable homoleptic iron carbonyl complexes, pentacarbonyliron, nonacarbonyldiiron and dodecacarbonyltriiron.

2.1.1 Iron carbonyl diene complexes

Iron carbonyl complexes are of special interest in organoiron chemistry, due to their high stability and with an iron(0) center capable of coordinating to complex organic ligands. One important class of complexes that has been used for a wide range of synthetic applications is iron carbonyl diene complexes.[114–120] A classic synthetic protocol for accessing such complexes starts from iron pentacarbonyl, where two carbonyl ligands are replaced by the diene system in a stepwise fashion. The dissociation of the first CO ligand requires rather high temperatures, around 130 - 140 °C, but can also be performed via photolytic dissociation.[109,121] Upon coordination to the iron carbonyl moiety, non-conjugated dienes isomerize to the corresponding conjugated iron carbonyl diene complex (Scheme 12). This rearrangement has been applied to a large number of 1,4-cyclohexadienes obtained via the Birch reduction.[122–124] Complexation of 1,3-dienes using iron nonacarbonyl can be achieved under milder conditions, typically by heating at around 50 °C,[44,121] or as low as room temperature.[125]

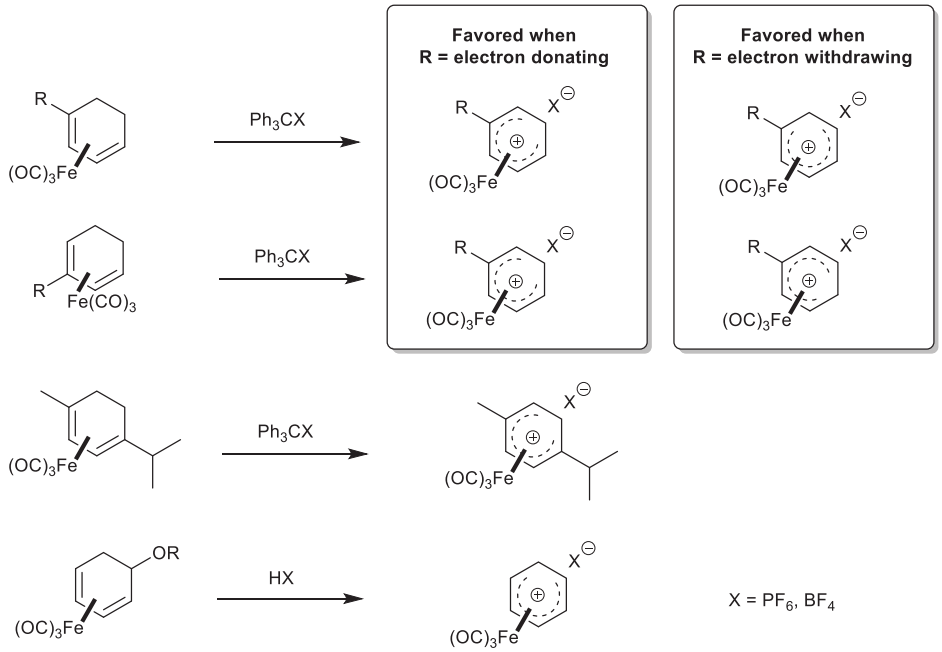


Scheme 12 Birch reduction followed by iron complexation of the formed 1,4-cyclohexadiene.

Iron coordination of a diene drastically alters its reactivity. The coordinated diene moiety is for example unreactive toward hydrogenation, hydroboration, dihydroxylation and Diels-Alder cycloadditions.[126,127] The iron carbonyl moiety also serves as a stereodirecting group, blocking one face of the diene with its steric bulk.[117]

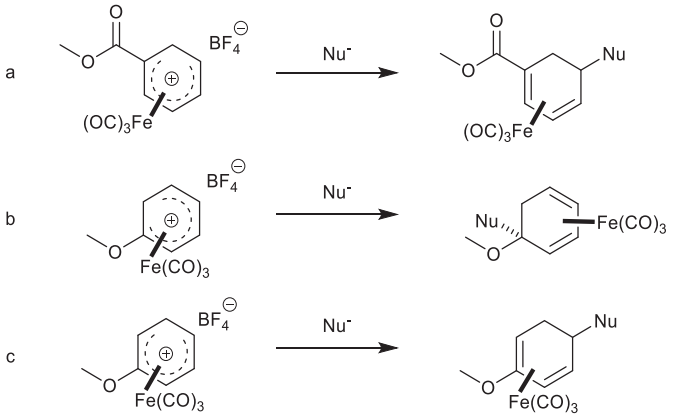
Iron carbonyl complexes of non-symmetrical dienes possess a plane of chirality and optically pure complexes can be obtained by diastereoselective complexation of enantiopure ligands. The optically pure complexes can also be obtained using optical resolution,[119,128] by enzymatic resolution[129] of the racemic compounds, or by using a chiral tricarbonyliron transfer reagent.[130] Knölker has developed a method for catalytic asymmetric complexation using a chiral 1-azabutadiene as an iron carbonyl transfer reagent.[131]

Coordination of an iron carbonyl moiety to a cyclohexadiene activates the compound for hydride abstraction by a triphenylcarbenium cation, forming a cationic η^5 iron carbonyl complex (Scheme 13).[132] The hydride is abstracted from one of the non-coordinating carbons from the face opposite to the iron carbonyl group, and the regioselectivity of the cation formation is governed by the substitution pattern of the diene. Electron withdrawing groups will direct the hydride abstraction to the *meta* position, while electron donating groups will favor abstraction from the *ortho* and *para* positions (Scheme 13).[44] Steric factors also affect the cation formation, directing the hydride abstraction by the bulky trityl cation to the least hindered position. The same types of cationic structures can also be formed by treating an iron diene complex containing a leaving group such as an alkoxy- or acetoxy group with an acid.[133] The cation can, in most cases, be precipitated as a fine powder to be used as a shelf-stable electrophilic building block. The most common counterions used are tetrafluoroborate and hexafluorophosphate, where the two salts show close to identical reactivity. However, some substituted cyclohexadienyl cations do not produce easily crystallizable tetrafluoroborate salts, instead precipitating as gums of lower purity. In many cases this can be solved by forming the more easily precipitated hexafluorophosphate salt.[44] One noteworthy approach to forming a chiral cationic cyclohexadienyl compound, is the use of a chiral trityl cation for hydride abstraction on a meso compound, demonstrated by Pettus, although the enantioselectivities obtained were modest.[134]



Scheme 13 Selectivity in the synthesis of cationic η^5 iron carbonyl dienyl complexes by hydride abstraction and leaving group dissociation.[44]

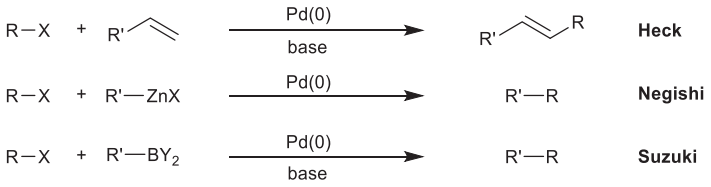
Cationic iron carbonyl cyclohexadienyl complexes are versatile iron-based building blocks for organic synthesis. They are powerful electrophilic carbocations, and among the most stable and easy to handle organometallic complexes.[44] As an example of their remarkable stability, cations that have been stored for ten years, open to air in a dark cupboard, were used in this project with no noticeable decrease in quality. The cationic complexes react with a broad range of nucleophiles, such as alcohols,[135] amines,[136] amides,[137] azide,[138] hydride,[138] carbamates,[119] thiols,[139] enolates,[136] allyl silanes,[140] electron rich aromatics[141] and heteroaromatics,[142] organocuprates,[136] organolithium[143] and organozinc reagents,[144] Grignard reagents,[136] phosphines,[145] and phosphites.[120] The addition of nucleophiles to the cation takes place stereoselectively at the opposite face to the iron carbonyl moiety, and regioselectively at one end of the conjugated dienyl. Substituents on the cation can act to direct the nucleophilic addition to either termini of the dienyl system, where electron withdrawing groups will generally favor addition in the *meta* position (Scheme 14, a),[44,146] and electron donating groups will direct nucleophilic addition to the *ipso* or *para* positions (Scheme 14, b and c).[147,148]



Scheme 14 Examples of regioselectivity in nucleophilic addition to cationic η^5 iron carbonyl dienyl complexes.[44]

2.2 Palladium-catalyzed cross-coupling reactions

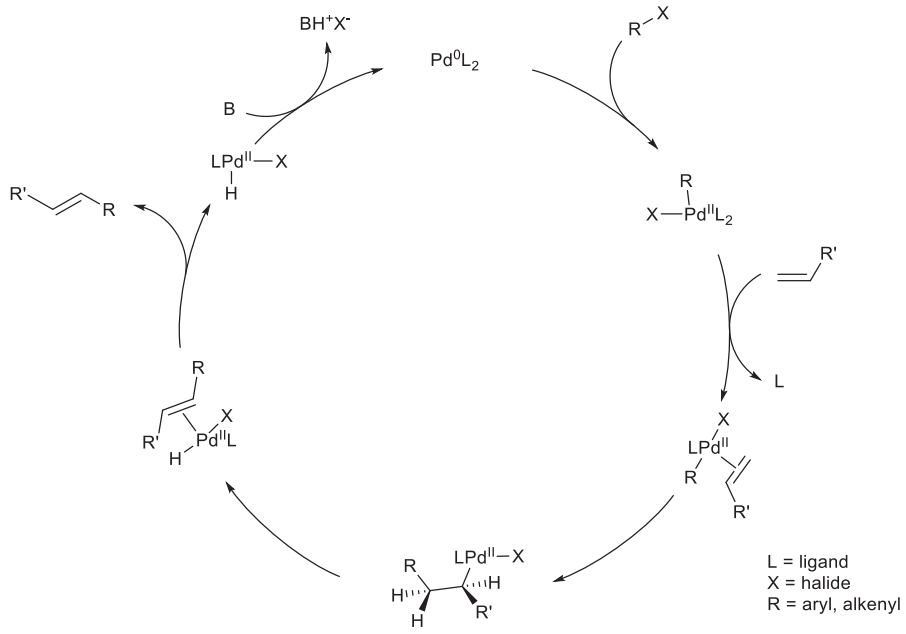
Metal-catalyzed coupling reactions are among the most useful transformations in organic chemistry. Although many metal centers can mediate such reactions, the palladium-catalyzed versions are arguably one of the most versatile tools available to an organic chemist. Much of the groundwork for palladium-catalyzed couplings was laid in the 1970s, when it was discovered that the use of palladium catalysis could drastically improve the selectivity and substrate scope over the classic metal-mediated cross- and homocoupling reactions.[38] The field has since then found widespread applications, and in 2010, the Nobel Prize in chemistry was attributed to Richard. F. Heck, Ei-ichi Negishi and Akira Suzuki, for their contributions to the field (Scheme 15).



Scheme 15 The Heck, Negishi and Suzuki reactions are examples of palladium-catalyzed cross coupling reactions.

2.2.1 The Heck reaction

Heck pioneered in the field of palladium-catalyzed cross couplings when he published his results on the coupling of organomercury compounds and alkenes in the presence of lithium chloropalladate.[149] Due to the high toxicity of the organomercury reagents, alternative methods were desired. Independent discoveries by Mizoroki[150] and Heck[151] demonstrated the coupling of aryl halides with olefins using catalytic palladium(II) salts, and this has since become known as the Mizoroki-Heck reaction, or just the Heck reaction.[152] The mechanism of the reaction proceeds via a catalytic cycle (Scheme 16) which starts with an oxidative addition of the organohalide to a neutral palladium species, subsequent insertion of the alkene (carbopalladation), forming the new C-C bond, followed by β-hydride elimination to form the product. The palladium(0) catalyst is then regenerated with the help of a base. This makes the reaction a formal C-H activation process, providing a higher atom economy than many other cross coupling reactions that rely on a transmetallation step.

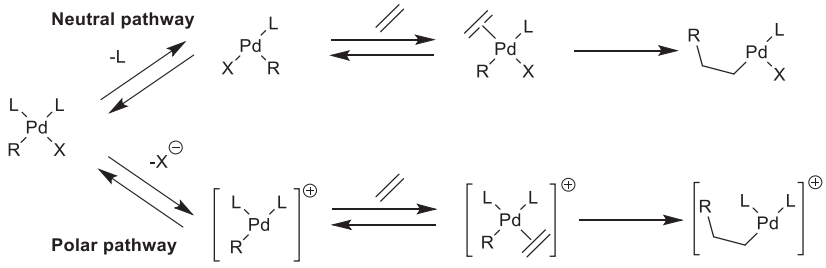


Scheme 16 The catalytic cycle for a Heck reaction.[153]

The classic scope of the reaction includes a variety of aromatic, heteroaromatic, vinylic and benzylic halides or triflates, to be coupled with both electron rich and electron poor olefins with a wide functional group tolerance.[153]

Ligands are commonly employed to modify the reactivity of the catalytic system. In addition to changing the electronic and steric environment around the palladium center, ligands can also assist in solubilizing and stabilizing the active palladium(0) catalytic species. If not properly stabilized, Pd(0) is prone to precipitating as elemental palladium, commonly referred to as palladium black.[154] Highly stabilizing ligands can also reduce the activity of the catalyst. Finding the right conditions where the active catalyst is reactive enough to perform the desired reaction, but also stable enough to suppress the precipitation as palladium black, can be a challenge when optimizing a Heck reaction.[152] The most common class of ligands are phosphines, but a wide range of ligands have been employed, including phosphites[155] and *N*-heterocyclic carbenes.[156] Another way of stabilizing the catalyst under "ligand free" conditions is to saturate the solution with a halide salt (some non-halide salts have also been successfully employed), often in the form of a tertiary alkylammonium salt. These conditions were developed by Jeffery in 1984[157,158] and are therefore commonly referred to as Jeffery conditions.

The Heck reaction can proceed via two different routes, outlined in Scheme 17. In the nonpolar (or neutral) route, the reaction is initiated by the dissociation of a neutral ligand and the anion is not lost until in the final reductive elimination step. The other possible route, called the polar (or cationic) mechanism, is initiated by the loss of the anionic ligand.[159] The polar path can be promoted by the use of bidentate neutral ligands and polar solvents, as well as by the addition of a halide scavenger such as a silver salt, or by the use of an aryl triflate coupling partner.[152]



Scheme 17 The neutral and polar pathways for the Heck reaction.

The neutral and polar mechanisms show different selectivities in the carbopalladation step, which is responsible for the regioselectivity of the reaction.[160] While the neutral mechanism is generally under steric control, producing branched substrates, the polar mechanism operates under a stronger electronic control, favoring arylation on the carbon with lower charge density. Examples of selectivities for the neutral and polar Heck-mechanism are shown in Figure 8.[159,161]

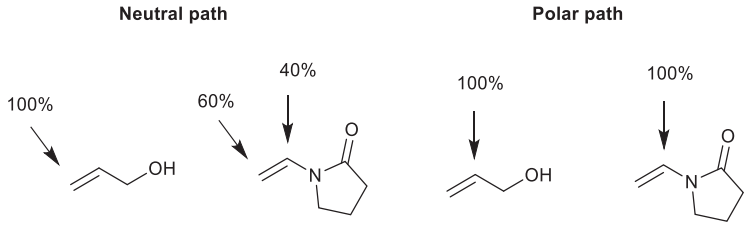
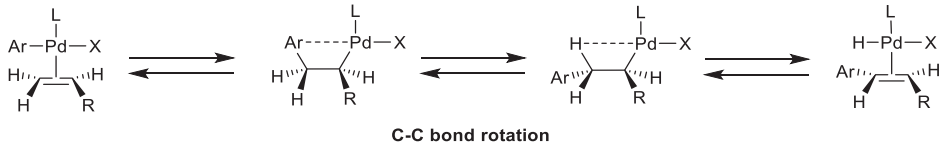


Figure 8 Examples of selectivity for the arylation of some olefins following the neutral and polar Heck reaction pathway. Arrows show selectivity for the indicated position.[159]

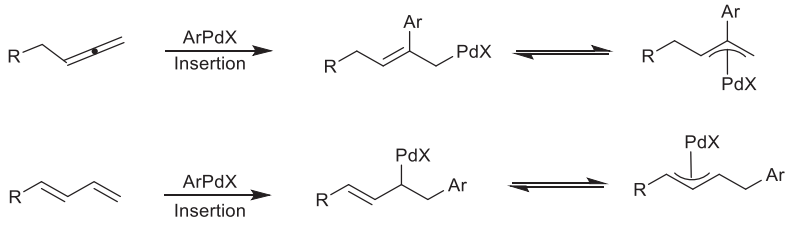
The insertion of the aryl coupling partner into the olefin, as well as the β-hydride elimination, both have to occur in a *syn* fashion, i.e. with the palladium coplanar to the aryl group or the hydride.[162] This means that in order to form the most common Heck-products, where the β-hydride elimination occurs at the same carbon as the arylation, a C-C bond rotation has to take place first (Scheme 18). For steric reasons, the aryl group will tend to eclipse the smallest substituent on the adjacent carbon in the elimination step, favoring *trans* products.[153]



Scheme 18 Stereochemistry in the insertion and the β-hydride elimination step of the Heck reaction.

In the case of a cyclic olefin, the rotation around the C-C bond is restricted and β-hydride elimination cannot occur on the same carbon as the insertion. If another β-hydrogen is present, this will lead to the formation of non-conjugated products.[163,164] Although the carbopalladation step is in most cases viewed as being irreversible,[165] it has been shown that alkene extrusion via β-carbon elimination can in some cases occur if there are no accessible β-hydrogens.[166,167]

When the olefin coupling partner is a 1,2- or 1,3-diene, the carbopalladation can result in a species where the palladium is connected to the carbon adjacent to an alkene. In this case, a π-allyl system will form (Scheme 19).[168]

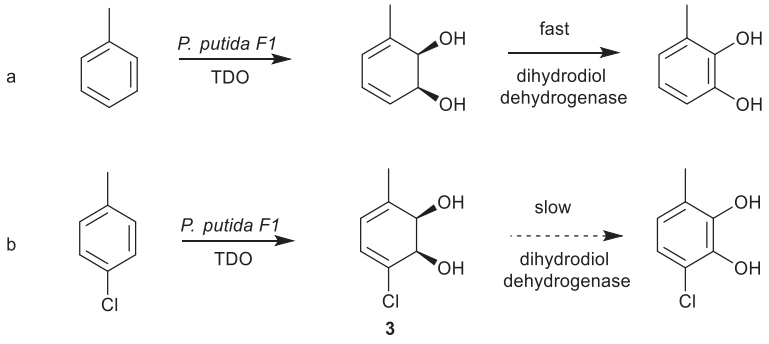


Scheme 19 Formation of a π-allyl system via the insertion of a diene.

The formed palladium π-allyl system can then react with a nucleophile in a Tsuji-Trost[169] type reaction, or reinstallation of an alkene via β-hydride elimination can take place if no nucleophile is present.[170]

2.3 Dearomatizing microbial arene *cis*-dihydroxylations

Biocatalysis, i.e. enzyme-catalyzed reactions, is often able to provide easy access to products which would be difficult or impossible to obtain using conventional synthetic methods. One such process which has been exploited synthetically is microbial arene oxidation (MAO). In particular, dearomatizing *cis*-dihydroxylation has found widespread use.[171] Over fifty years ago, Gibson reported the first isolation of a *cis*-dihydrodiol metabolite, obtained when investigating the oxidation of a number of haloarenes by *Pseudomonas putida* F1.[172] This strain had previously been shown to rapidly oxidize benzene to catechol. Gibson proposed a pathway involving the initial formation of a *cis*-dihydrodiol, which rapidly undergoes an enzyme-catalyzed rearomatization to the catechol (Scheme 20, a).[173] When haloarenes were used as substrates, the rearomatization step proceeded at a lower reaction rate and the intermediate could be isolated (Scheme 20, b). The dearomatized product obtained from oxidation of *p*-chlorotoluene was found to be optically active and was identified as *cis*-diol **3**.

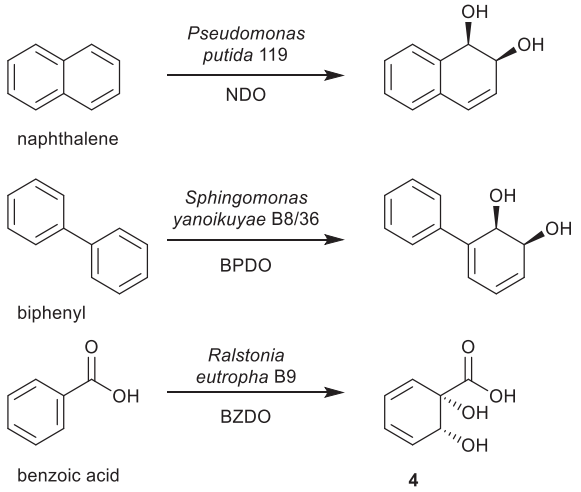


Scheme 20 Action of Pseudomonas putida F1 on toluene and p-chlorotoluene.[173]

A mutant strain, *Pseudomonas putida* F39/D, where the gene coding for the dihydrodiol dehydrogenase enzyme responsible for rearomatization of the dihydrodiol is inactivated, was

developed in 1970.[174] This opened up for more convenient synthesis of a larger scope of dearomatized products without the risk of overoxidation.[171]

The enzyme expressed by *P. putida* F39/D, responsible for the dearomatization, is known as toluene dioxygenase (TDO). After the initial report of *P. putida* F1, other organisms expressing different arene dioxygenases have been described.[171] These organisms are capable of catalyzing similar reactions, but with different selectivities and substrate scope. Although many arene dioxygenases are known, the ones which have been most extensively exploited for synthetic purposes are TDO and naphthalene dioxygenase (NDO) expressed by *P. putida* 119,[175,176] biphenyl dioxygenase (BPDO) expressed by *Sphingomonas yanoikuyae* B8/36[177] and benzoic acid dioxygenase (BZDO) expressed by *Ralstonia eutropha* B9[178] (Scheme 21). The action of BZDO is unusual as it catalyzes an *ipso, ortho* dihydroxylation relative to the benzoic acid moiety, producing products with a quaternary stereocenter as in MAO-product **4**.



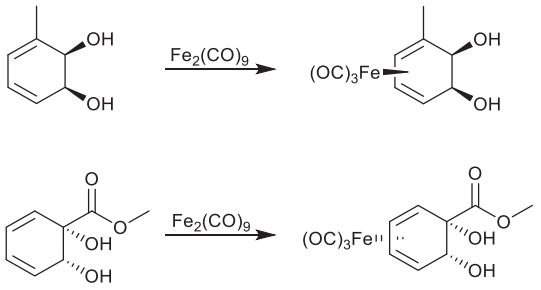
Scheme 21 Action of the arene dioxygenases expressed by P. putida 119, S. yanoikuyae B8/36 and R. eutropha B9.

These microbial arene oxidations are an efficient way to introduce complexity which can be used for further chemical transformations. In a single synthetic step, an enantiomerically pure product containing two chiral stereocenters is obtained. At the same time, useful synthetic handles which can be exploited for selective chemical transformations, are introduced.

The use of these "wild-type" mutant strain organisms for biotransformations does however suffer from some drawbacks. Although the organism is inactivated, it will still have the gene coding for the dihydrodiol dehydrogenase, responsible for rearomatization of the formed dihydrodiol. There is a risk that it will be reactivated by a spontaneous mutation, resulting in decomposition of the desired diol product.[171,179] Another disadvantage is that in order to start producing the relevant enzyme, these mutant strains need to be induced by the addition of a substrate known to induce the enzyme expression. In many cases, the expression can be induced by the substrate itself, but some aromatics might be viable substrates for the oxidation without acting as inducers. In these cases, a separate inducer needs to be added at the beginning of the transformation.[171] These problems can be solved by creating recombinant organisms, by cloning the relevant genes into a host organism, usually *Escherichia coli*.[180] The new recombinant strain will lack the genes coding

for the dihydrodiol dehydrogenase, and the enzyme can be expressed without the addition of an arene as inducer.

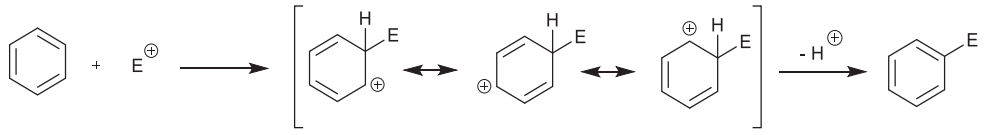
As mentioned earlier, the stereoselectivity in the iron carbonyl complexation to a cyclohexadiene is influenced by its substitution pattern. One case where excellent stereocontrol is observed is when lewis basic substituents are present on one or both sp^3-centers. The coordination of the iron carbonyl moiety is in this case directed to the face syn to the lewis basic group. The facial selectivity has been rationalized by the reaction proceeding through precoordination of a tetracarbonyliron fragment to an alcohol oxygen. This has been shown to give complete stereoselectivity in iron carbonyl complexations to cyclohexadiene 1,2-cis diols obtained from microbial arene oxidations, producing enantiopure iron carbonyl complexes (Scheme 22).[181,182]



Scheme 22 Synthesis of chiral iron carbonyl diene complexes from microbially derived cyclohexadienes.[181,182]

2.4 Electrophilic aromatic substitution

Aromatic molecules have the ability to react with electrophiles in what is called an electrophilic aromatic substitution (Scheme 23).[183] The reaction is initiated by a nucleophilic attack on the electrophile by the π-system of the arene, creating a carbocation intermediate. This intermediate, although highly reactive, gains some stability from resonance delocalization of the cation between the *ortho* and *para* positions. Loss of a proton from the intermediate carbocation restores the aromaticity of the system, forming the product, the overall result being substitution of a hydrogen by an electrophile.[183]



Scheme 23 The electrophilic aromatic substitution reaction.

Electrophilic aromatic substitution reactions are widely used in industry, for instance in the production of ethylbenzene[184] or for the nitration of aromatics.[185] These reactions usually require the use of harsh conditions or powerful electrophiles that are often generated in situ.

The substituents on the aromatic ring will influence its reactivity towards electrophiles by affecting its electronic properties.[183] Electron donating groups will donate electrons to the aromatic ring, making it more reactive towards electrophiles, while electron withdrawing groups will draw electron density from the system making it less nucleophilic (Figure 9).

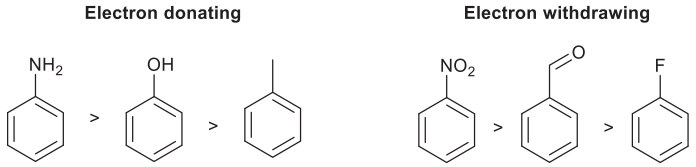


Figure 9 Examples of arenes possessing electron donating and electron withdrawing groups.

There are two main ways that a substituent can affect the electron density of an aromatic ring, via inductive effects or through resonance.[153] The inductive effect acts by the withdrawal or donation of electrons through sigma bonds, and is largely related to the electronegativity of the substituent. Resonance effects involve the donation or withdrawal of electrons by conjugation with the π-system of the aromatic (Figure 10).

Figure 10 Resonance structures of aniline and nitrobenzene showing electron donation and withdrawal through resonance.

In addition to the effect on the reaction rate, the substituents can also have a directing effect on the addition.[153] An electron donating group will be able to stabilize the cationic intermediate from *ortho* or *para* attack in the substitution reaction, while an electron withdrawing group on the other hand will destabilize these intermediates (Figure 11). As a result, substituents able to donate electrons through resonance will direct the electrophile to the *ortho* and *para* positions, while electron withdrawing substituents will be *meta* directing.

Figure 11 Stabilization and destabilization of the cationic intermediate formed in an electrophilic aromatic substitution, by an amine and nitro group respectively.

It is possible for a group to be electron withdrawing by induction, and at the same time electron donating by resonance.[153] Halides, for example, serve to deactivate the aromatic system by induction, reducing its reaction rate in electrophilic aromatic substitution reactions, while at the same time acting as *ortho/para* directing by resonance stabilization from lone pair electrons.

Many heteroaromatic molecules also display C-nucleophilicity, one example being indole. The nitrogen can stabilize a cationic intermediate by donating its lone pair into the aromatic system (Figure 12).[186] The 3-position is the preferred site of addition, as the cationic intermediate formed can be stabilized without disrupting the aromaticity of the benzene ring.

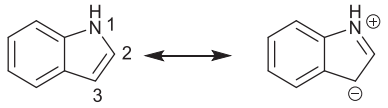


Figure 12 Resonance structures of indole, showing a polarization towards the nucleophilic 3-position.

Azulene is an interesting case, where the unusual structure of this hydrocarbon results in a surprisingly high nucleophilicity. As the π-electrons of azulene are polarized towards the five membered ring to achieve Hückel aromaticity, it gives the azulene some character of a cyclopentadienyl anion, fused to a tropylium cation (Figure 13).[74] The most nucleophilic sites are the 1- and 3-positions since, as in the case of indole, addition at these positions can be stabilized without disrupting the aromaticity of the neighboring ring.[187]

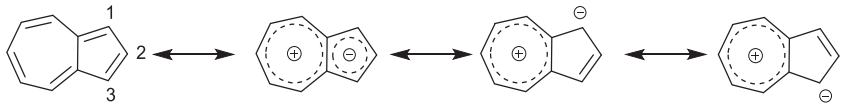


Figure 13 Resonance structures of azulene, showing a polarization towards the nucleophilic 1- and 3-positions.

2.5 Modelling reactions using computational chemistry

Computational chemistry provides the tools to calculate the energies of not only persistent molecules, but also molecules representing short lived intermediates.[188] Even fleeting structures with a lifetime no longer than the timescale of the molecular vibrations which creates them, such as the transition states which connect the reactants and products of a chemical reaction, can be modelled. These models can then be used to map out reaction pathways, for example to gain insight into the mode of action of catalysts, information which can then be used to develop improved versions of the catalyst.[69]

2.5.1 Geometry optimizations

With the tools to calculate the energy of a given molecular assembly, comes the ability to perform geometry optimizations. These rely on the Born-Oppenheimer approximation, which states that the electrons and nuclei in a molecule can be treated separately.[189] This allows us to use a nuclear structure as input, and calculate the electronic energy using a method such as DFT or ab initio calculations. Upon calculating the energy of, and forces acting upon, an input structure (a guess for the final structure you are looking for), the molecular structure can then be varied until a minimum energy conformation is found.[69] The relation between molecular (nuclear) structure and energy is called the potential energy surface (PES). After a successful geometry optimization, the resulting structure will correspond to a local minimum on the PES, which means that any small

adjustment in the molecular geometry will increase the potential energy of the molecule, resulting in a stable structure.

2.5.2 Modelling transition states

The method used for geometry optimizations can also be used to locate a transition state structure, which is characterized by a the saddle point on the PES.[188] On the PES, a saddle point means movement in every direction but one will result in an energy increase, while one direction is at a local energy maximum. The saddle point represents a transition state structure, and the trajectory leading down on either side of the saddle point is called the reaction coordinate. At the saddle point, the transition state structure will therefore be at an energy maximum along the reaction coordinate, and can either proceed over the maximum, or fall back into its pre-reaction state. The ability to locate transition states, as well as stable intermediates, is the key to being able to map out reaction paths using computational chemistry.

2.5.3 Mapping out reactions

By modelling the relevant reactants, transition states, intermediates and products in a reaction, a reaction path can be mapped out. This is often presented as an energy profile, i.e. a graph showing the energy of the relevant structure as it proceeds along the reaction coordinate.[190] This allows us to calculate energy barriers, and by modelling competing transition states, different mechanistic paths can be compared.

3. Aim

The work presented in this thesis concerns the development of selective transition metal-mediated chemical transformations, using bio-derivable starting materials.

The aims of the thesis are

- To develop chemistry that is adapted to the use of renewable starting materials and naturally occurring structural motifs.
- When possible, optimize these reactions to be able to proceed using greener conditions.
- Use the developed methods to create structurally complex intermediates for use in further synthesis or to form new chemicals with potentially interesting properties.

4. Nucleophilic additions to cationic iron carbonyl complexes

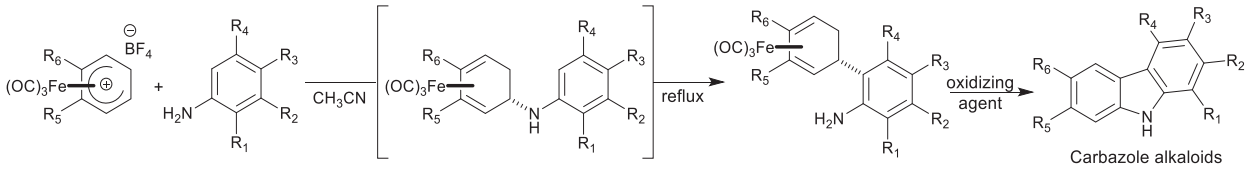
Cationic η^5 iron carbonyl dienyl complexes are powerful and versatile electrophiles, capable of reacting with a broad range of nucleophiles under mild conditions.[118] The addition of electron rich aromatic and heteroaromatic systems to yield *C*-addition products is quite a well explored area.[44] These reactions proceed through an electrophilic aromatic substitution mechanism with highly activated aromatic substrates such as oxygenated arenes,[141] furan,[142] indole[142] and aniline.[191] The additions often proceed smoothly under mild conditions at ambient temperature, generally in the presence of a base. In some cases, the addition is known to proceed without the aid of a base, producing the corresponding acid of the anion in question.[142] Similarly, the addition of many heteroatom nucleophiles such as alcohols[135] and amines[136] are well documented.

Cationic iron carbonyl complexes have found many synthetic uses[109,118] for example in the synthesis of oseltamivir,[119,120] and a wide range of carbazole alkaloids.[192–194] Although the range of compatible nucleophiles in these types of reactions are relatively well investigated, there are some unexplored opportunities to expand the scope of the reaction.

4.1 Phenolic nucleophiles in the addition to a cationic iron carbonyl complex (Paper I)

There are many natural sources for phenolic molecules[195,196] such as lignin or other abundant biomass resources.[22,23] Despite this, phenols have not been extensively studied as nucleophiles in addition reactions to cationic iron carbonyl dienyl complexes. Phenols have two different types of nucleophilic reactivity, they can undergo both *O*-addition[197,198] and *C*-addition.[199]

Like phenols, anilines also have two different types of nucleophilic sites in the form of an amine and an activated aryl position. This reactivity has been thoroughly investigated in the reaction with cationic iron carbonyl cyclohexadienyl complexes.[44] When an iron carbonyl dienyl cation is treated with aniline at room temperature, the *N*-addition product is obtained. Performing the same reaction under reflux in acetonitrile yields the *C*-addition product. The same product is also formed upon heating the *N*-alkylated product, this shows an example of kinetic versus thermodynamic control.[137] This reactivity has been extensively exploited in natural product synthesis by Knölker, to access a variety of carbazole alkaloids by *C*-addition of a substituted aniline, followed by oxidative cyclization, decomplexation and aromatization, as seen in Scheme 24.[200–202]



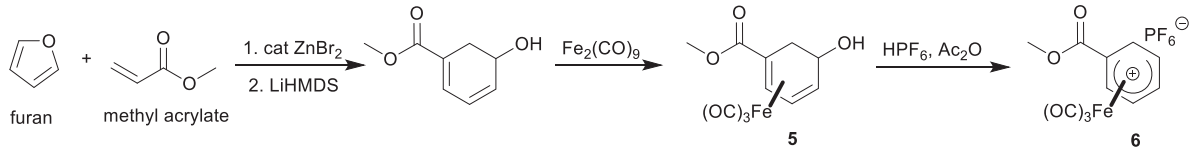
Scheme 24 Iron carbonyl-based synthesis of carbazole alkaloids.[202]

In contrast to anilines, the selective *C*- or *O*-addition of phenols has not been previously investigated, and no method for directing the addition of a bidentate nucleophile selectively towards either *C*- or *O*-addition has been reported. This encouraged us to investigate the reactivity

of a range of naturally occurring phenols in the nucleophilic addition to a cationic iron carbonyl cyclohexadienyl complex.

4.1.1 Choice of model system

Cationic complex **6**, produced by acid-mediated cation formation from neutral complex **5**, was chosen as the electrophile for the study. The substrate was selected because it could be easily synthesized from a cycloaddition product of furan and an acrylate ester, both potentially available from renewable sources (Scheme 25).[203–206]



*Scheme 25 Synthesis of cationic complex **6**.*

Sesamol was chosen as a model nucleophile for the optimization studies. Sesamol is naturally available from sesame oil[207] and can potentially undergo both *O*-addition and *C*-addition (Figure 14).

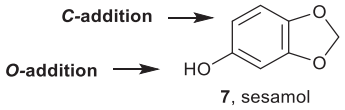
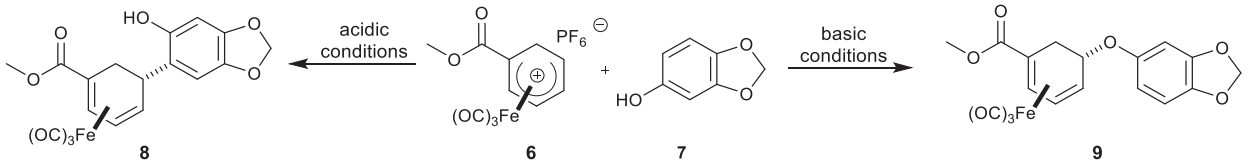


Figure 14 Structure and nucleophilic sites of sesamol.

Initial tests showed that sesamol (**7**) underwent selective *C*-addition to cationic complex **6**, forming **8** when no base, or a polymer bound amine base, was added. The addition of a homogeneous base instead afforded *O*-addition product **9** (Scheme 26). This selectivity was proposed to arise from a fast and, under acidic conditions, reversible *O*-addition, where **9** can be trapped by the addition of a base, competing with a slower but irreversible *C*-addition, forming **8**.

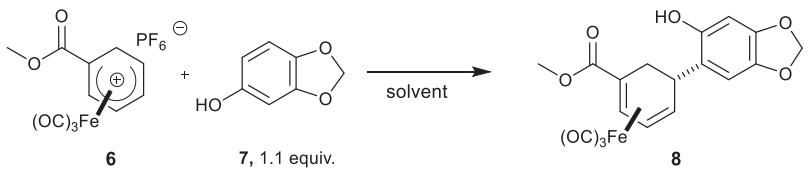


*Scheme 26 Reactivity of sesamol with cationic iron carbonyl complex **9**.*

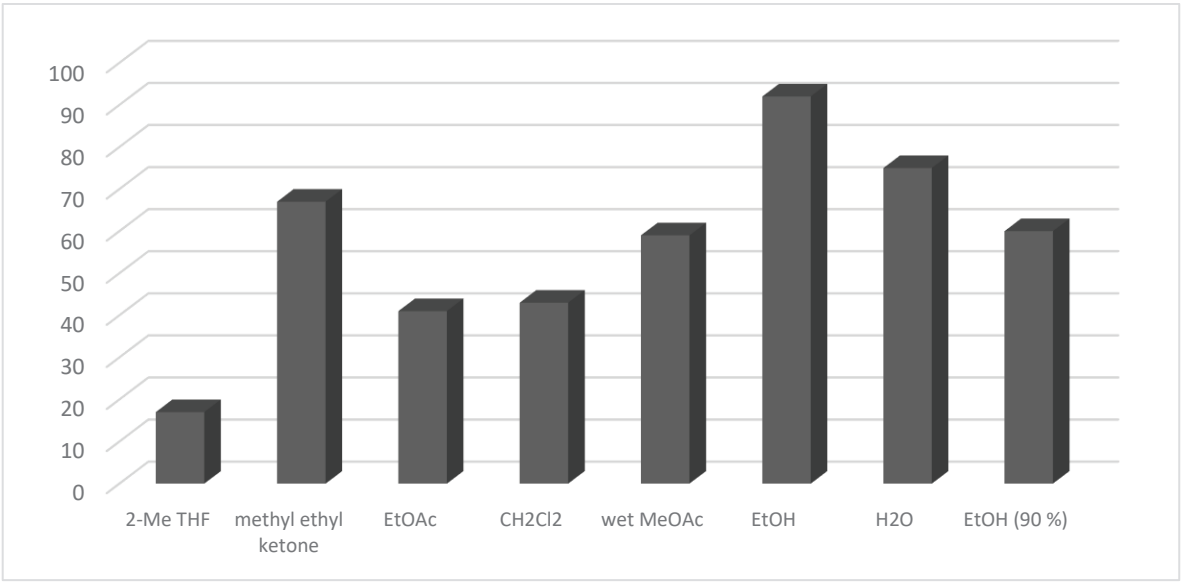
4.1.2 Optimization and selective *C*- or *O*-addition of phenolic nucleophiles

When optimizing the reaction, we prioritized the use of green and sustainable conditions. Yields were evaluated by quantitative NMR using an internal standard (*p*-xylene) as reference. The *C*-addition, was optimized using base-free conditions and we started out by screening a number of green solvents,[208] seeking to find an alternative to solvents like dichloromethane, acetonitrile and tetrahydrofuran, commonly used for these types of reactions. A summary of the solvent screening is found in Table 1.

Table 1 Results from the solvent screening for the C*-addition of sesamol to cationic complex* ***6****, yields quantified by NMR.*



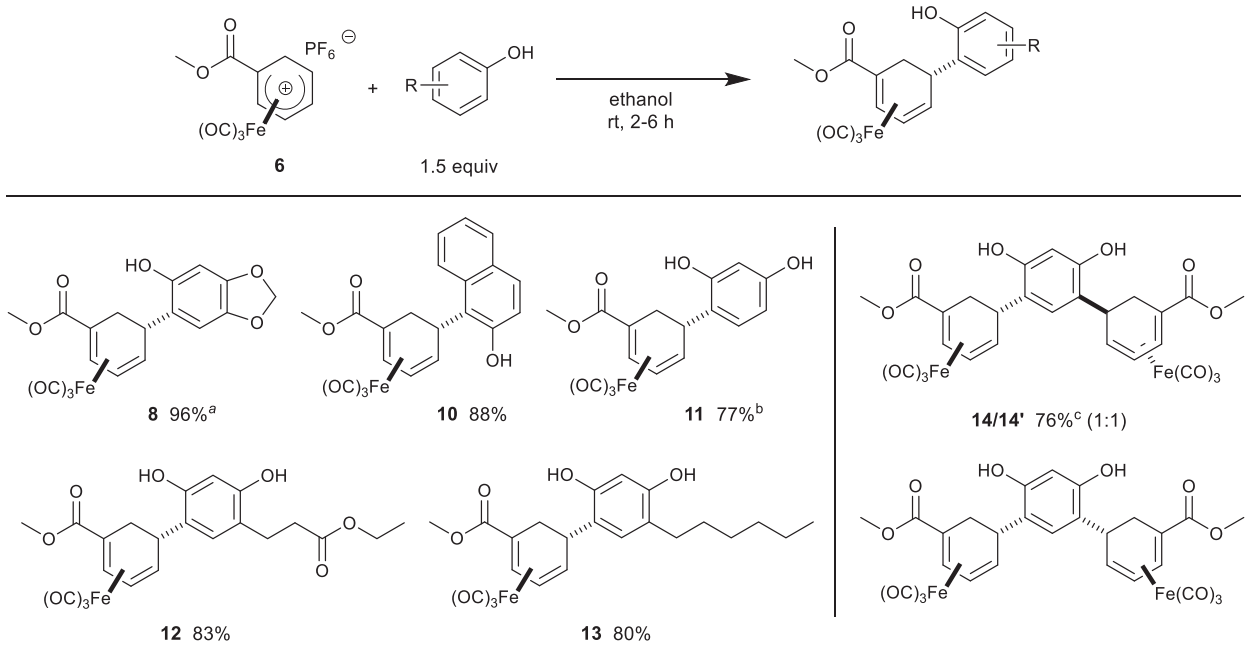
6 **7,** 1.1 equiv. **8**



We were happy to see that the best solvent we found was ethanol, a benign solvent readily available from renewable sources,[208,209] and under these conditions the *C*-addition product was obtained in 92% yield. Water also worked well, giving a 75% yield of the product. In this case the lower yield may to some extent be attributed to the low solubility of the product, producing a sticky precipitate which trapped some of the starting materials. In ethanol, the reaction could be visually monitored by the disappearance of the starting material that initially formed a light-yellow turbid suspension. As the reaction proceeds, the solution gets clearer since the product is soluble in ethanol. The reaction in water could be improved by performing the reaction with more vigorous stirring, forming a light-yellow precipitate that could be easily isolated by filtration. Product **8** was obtained in 89% yield after purification with flash column chromatography.

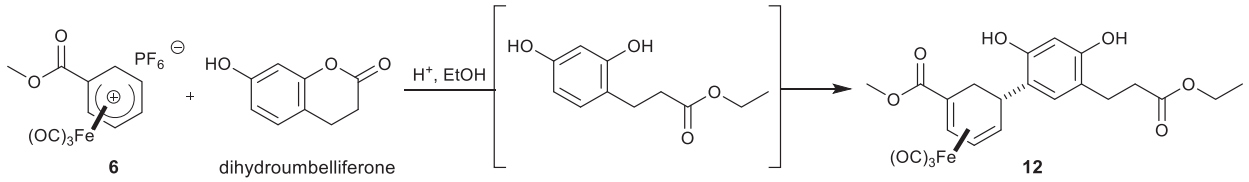
The optimized conditions were used to synthesize a number of *C*-addition products from electron rich aromatic nucleophiles, with a focus on naturally occurring compounds. The *C*-addition reactions proceeded smoothly with phenols activated by a hydroxyl or methoxy substituent in the *meta* position, such as sesamol and 4-hexylresorcinol, affording **8** and **13** in good yields (Scheme 27). Reaction with 2-naphthol gave selective substitution at the 1-position, affording product **10** in good yield. Reaction with resorcinol yielded both the mono addition product **11** and the double addition product **14/14'**, where the latter was formed as a mixture of the two diastereomers in equal proportions. However, through variation of stoichiometry, the reaction could be tailored to selectively afford either the mono- or the disubstituted product.

The non-phenolic activated aromatic 1,3-dimethoxybenzene also underwent a successful addition although at a slower rate, yielding a mixture of mono- and disubstituted products.



Scheme 27 Successful C-addition products of phenolic nucleophiles. [a]1.1 equiv nucleophile. [b]5.0 equiv nucleophile. [c]0.5 equiv nucleophile.

Reaction with the 3-acetoxy-substituted phenol dihydroumbelliferone yielded the ring-opened resorcinol derivative **12**. The reaction likely proceeds through an initial transesterification with the ethanol solvent, followed by a *C*-addition of the more highly activated phenol formed (Scheme 28).



Scheme 28 Proposed reaction path for the reaction with dihydroumbelliferone.

Another phenol which gave successful *C*-addition, but where the product proved difficult to isolate, was 3-methoxyphenol, yielding an inseparable mix of products alkylated at the 2, 3, and 6 positions. 2-Methoxyhydroquinone also gave a successful addition, mainly in the 5-position, but the product proved unstable, most likely due to oxidation in air, forming an insoluble precipitate. Surprisingly, no reaction was seen for aromatics possessing a 1,2,3-*O*-substitution pattern such as syringol or 1,2,3-trimethoxybenzene under these conditions, possibly due to an inductive deactivating effect from the oxygen substituent in the meta position. Some other substrates which were tested but gave no *C*-addition products were naturally occurring eugenol, vanillin, umbelliferone, as well as 1-naphthol (Figure 15).

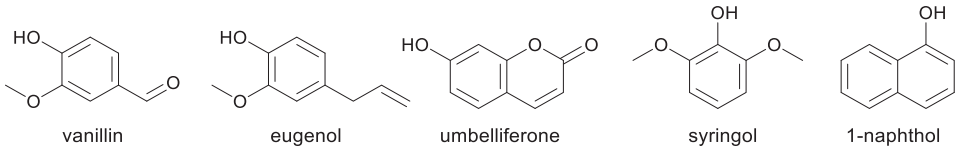
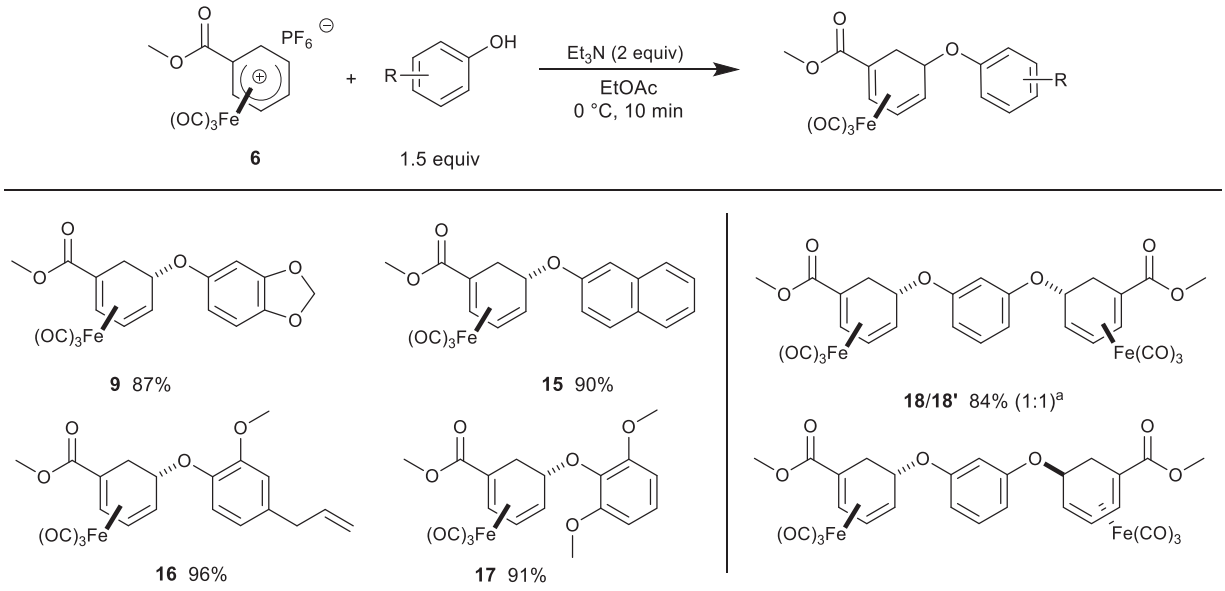


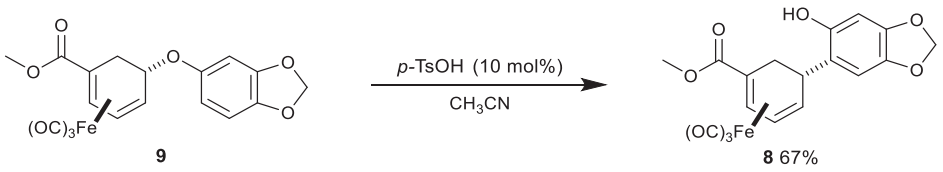
Figure 15 Phenolic nucleophiles that proved to be unreactive under the C-addition reaction conditions.

For the optimization of the *O*-addition, triethylamine was chosen as the base and, as with the *C*-additions, the screening focused on sustainable solvents. Only non-protic solvents were tried, as protic solvents such as alcohols or water can act as nucleophiles in the presence of a base. In this case, the reaction proceeded very rapidly, and after some initial inconsistent results, it was found that rapid addition of the base under vigorous stirring was key to improving the yield. The nucleophile was therefore first dissolved in the solvent along with the base before it was added to the cationic complex under vigorous stirring. The reaction mixtures changed from turbid to clear in a matter of seconds and a reaction time of two minutes was used for the screening. The results indicated that the *O*-addition reaction was less dependent on the solvent, producing *O*-addition product **9** with consistent yields of 80% in several polar aprotic solvents, along with some *C*-addition product. In less polar solvents, the yields were significantly lower, most likely due to solubility issues, as the formed triethylammonium hexafluorophosphate resulted in a sticky precipitate trapping some of the starting materials. Ethyl acetate was chosen for the continued optimization as it is benign and can be produced from renewable resources.[208,210] In order to suppress the formation of the *C*-addition product, the reaction was performed at 0 °C. This resulted in incomplete conversion after 2 minutes. However, upon increasing the reaction time to 10 minutes, a yield of 89% was achieved. These conditions were used to synthesize a number of *O*-addition products from the addition of phenolic nucleophiles to complex **6** (Scheme 29). 2-Naphthol performed well in the *O*-addition reaction as well, affording **15**. The substrate scope for the *O*-additions was broader than the *C*-additions, and both eugenol and syringol afforded *O*-addition products **16** and **17** in good yields. The stability of the products, however, seemed to decrease with increasingly electron deficient phenols. Resorcinol could be added to the complex and produced double addition product **18/18'** in good yield. No *O*-addition product from the mono-addition of resorcinol could be isolated.



Scheme 29 Successful O-addition products of phenolic nucleophile. [a]0.5 equiv nucleophile.

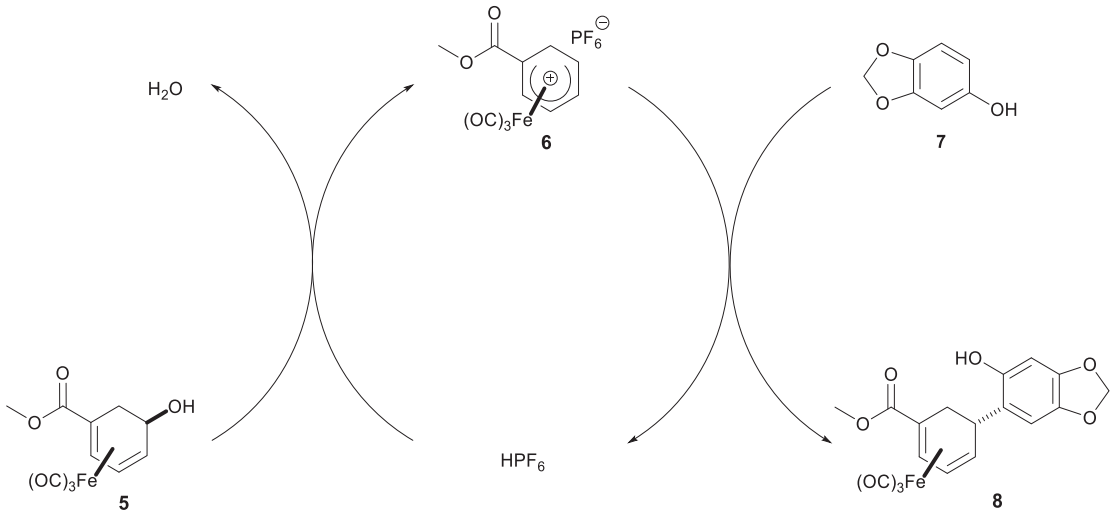
The *O*-addition products were also found to be acid sensitive. When product **9** was left overnight in deuterated chloroform, a rearrangement to the *C*-addition product **8** was seen (Scheme 30). When the solvent was filtered through a plug of basic aluminum oxide before use, no rearrangement was observed, indicating that the rearrangement was catalyzed by trace acid impurities in the solvent. This could be confirmed when a solution of the *O*-addition product in base-filtered solvent rearranged upon addition of catalytic *p*-TsOH.



Scheme 30 Acid-catalyzed rearrangement of O-addition product to C-addition product.

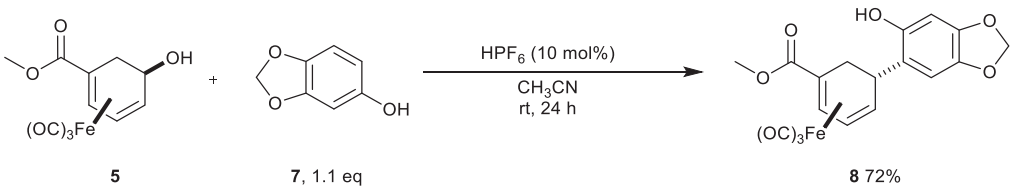
4.1.3 Acid-catalyzed synthesis of *C*-addition products

The acid-catalyzed rearrangement of *O*- to *C*-addition product encouraged us to try a more direct route to the *C*-addition products, starting from the neutral η^4 complex **5** without pre-forming the cationic η^5 complex (**6**), using catalytic acid (Scheme 31). We were happy to see that allowing the neutral complex to react with sesamol in acetonitrile, using 10% HPF_6 as a catalyst, afforded *C*-addition product **8** in 72% yield, comparable to the combined yield of the two-step reaction (74%).



Scheme 31 Proposed catalytic cycle for the formation of C-addition products directly from the neutral precursor complex.

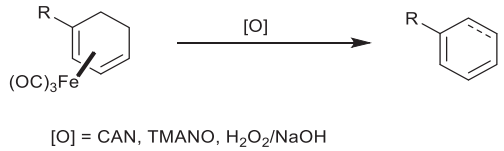
This new method eliminates one reaction step, where excess HPF_6 and acetic anhydride desiccant is used to form the cationic complex, which is precipitated using large quantities of ether. The atom economy of the reaction is improved from 61% to 93%, providing a more efficient and green synthetic protocol (Scheme 32). The catalytic reaction could also be performed using less hazardous tetrafluoroboric acid,[211,212] which could not be used in the stoichiometric reaction due to difficulties in precipitating the corresponding tetrafluoroborate salt of cation **6**.[213] Using HBF_4 in the catalytic reaction produced similar yields to HPF_6.



*Scheme 32 Synthesis of the C-addition product **9** using catalytic acid.*

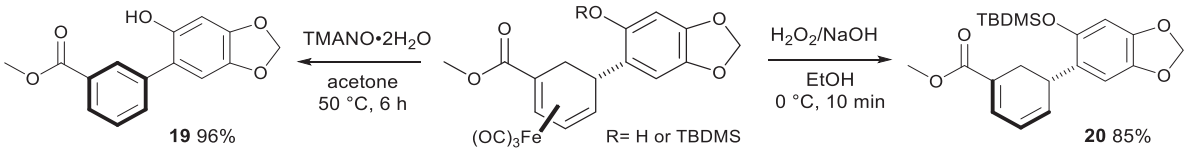
4.1.4 Decomplexation

In order to allow for a wider scope of applications, we wanted to access the corresponding demetallated products. To introduce further diversity, we aimed at finding selective conditions for demetallation of the product iron carbonyl diene complexes to the free diene, as well as to the aromatized product respectively. Several methods for the demetallation of iron carbonyl diene complexes exist and these usually proceed through oxidative removal of iron (Scheme 33). The most commonly used reagents are hydrogen peroxide under basic conditions,[214] ceric ammonium nitrate[215] (CAN) or trimethylamine *N*-oxide (TMANO).[216]



Scheme 33 Oxidative decomplexation of iron carbonyl cyclohexadienyl complex affording free diene or aromatized product.

Attempts at decomplexation of the *C*-addition product **8** using ceric ammonium nitrate or basic hydrogen peroxide resulted only in decomposition of the starting material. Decomplexation using the milder oxidant trimethylamine *N*-oxide was successful in yielding the aromatized product **19** in excellent yield (Scheme 34). The unsuccessful results using the stronger oxidants could possibly be attributed to oxidation of the phenol. In order to make it less sensitive to oxidation, it was protected as a *tert*-butyldimethylsilyl ether**.**



*Scheme 34 Demetallation to products **19** and **20**.*

Oxidative removal of the iron carbonyl moiety from the silyl ether using basic hydrogen peroxide or ceric ammonium nitrate afforded the free diene **20** in good yield (Scheme 34). Unfortunately, the *O*-addition products were too sensitive to tolerate the oxidative decomplexation conditions and all attempted demetallations using these three reagents resulted in decomposition of the starting material.

4.1.5 Summary and outlook

For the first time, a protocol for the selective *C*- or *O*-addition of phenolic nucleophiles to a cationic iron carbonyl dienyl complex has been reported. The scope of nucleophiles compatible with these types of reactions has been increased with several naturally occurring phenols and the additions have been performed using green reaction conditions. The *C*-addition reactions performed best in ethanol or water, with no added base at ambient temperature. For selective *O*-addition, the reaction was performed in ethyl acetate at 0 °C with triethylamine as a base. Decomplexation of a *C*-addition product was then demonstrated, selectively affording an aromatized product or a diene depending on the methodology used. Decomplexation of the *O*-addition products were unfortunately not successful. Additionally, a new method for forming the *C*-addition products directly from the neutral iron carbonyl precursor complex using catalytic acid is presented. This new method eliminates the need to isolate the cationic complex while significantly reducing the amount of solvent used. It also reduces the amount of acid used to form the cationic complex to catalytic amounts and eliminates the use of desiccant in the intermediate step, resulting in a significant improvement in atom economy.

This method provides access to products which could be of high value in synthetic chemistry. Synthesis of biaryls similar to **19** could potentially be produced using cross coupling reactions. For example, Schmidt has demonstrated Suzuki-Miyama coupling of a broad range of phenolic

halides and boronic acids.[217] This method, however requires access to pre-functionalized phenols, uses noble metal catalysis and harsher conditions than the techniques presented in this project. Non-noble metal catalysts have been developed for these types of transformations and similar structures could also be formed using for example nickel-catalyzed cross-coupling reactions[218], as well as C-H functionalizations where derivatization of the phenol is not necessary.[219,220] High temperatures are however still often required.

Substituted cyclohexadiene **20**, which could be produced by protection of the phenol followed by oxidative removal of the iron moiety, could be difficult to access by more conventional means. In this case, the high facial selectivity combined with the relatively easy accessibility of chiral iron carbonyl dienyl complexes from MAO-products opens up for highly selective synthesis of chiral products. Other methods can produce similar products, such as the catalytic phenol-directed Claisen rearrangement reported by Trost,[221] or the highly stereospecific palladium-catalyzed decarboxylative coupling of aryl iodides with 2,5-cyclohexadiene-1-carboxylic acids by Studer.[222] Although other methods to access this class of products exist, these can be viewed as complementary to the method presented here.

Out of the 12 principles of green chemistry, the following have been addressed in this project:

- 1. Prevent waste
    - The *C*-addition reactions can be performed without added base. Furthermore, in the acid-catalyzed protocol, the synthesis is shortened by one step, eliminating the need to isolate the intermediate. This greatly reduces the production of solvent waste.
- 2. Atom economy
    - The catalytic protocol provides an increase in atom economy from 61% to 93%.
- 3. Less hazardous synthesis
    - The catalytic reaction can be performed using less hazardous tetrafluoroboric acid.
- 5. Benign solvents and auxiliaries
    - The reactions have been developed with a focus on green solvents and the optimized conditions uses benign and potentially renewable ethanol or ethyl acetate.
- 7. Use of renewable feedstock
    - The cyclohexadiene scaffold was synthesized using starting materials which can be produced from renewable resources and the nucleophile scope is focused on naturally occurring phenols.
- 8. Reduce derivatives
    - The catalytic reaction eliminates the need of a stoichiometric derivatization, the formation of the HPF_6 salt of the dienyl cation.
- 9. Catalysis
    - The *C*-addition reaction can be performed using catalytic, rather than excess acid.

4.2. Azulene nucleophiles in the addition to cationic iron carbonyl complexes (Paper II)

Azulene (Figure 16) has not previously been investigated as a nucleophile in the addition to cationic η^5 iron carbonyl dienyl complexes, despite having a nucleophilicity similar to indoles[76] which readily add to this class of electrophiles.[142] Therefore, azulenes could be good candidates for expanding the scope of this reaction. While azulene itself is a quite expensive synthetic product, naturally occurring azulene derivatives exist. Of special interest is guaiazulene (Figure **16**), a naturally sourced azulene. Guaiazulene is used in cosmetics as a colorant and skin soothing additive, and its 3-sulfonate salt is used as an anti-ulcer agent.[223] Guaiazulene, being a large-scale commercial product is inexpensive and readily available, making it an attractive starting material for synthetic purposes.

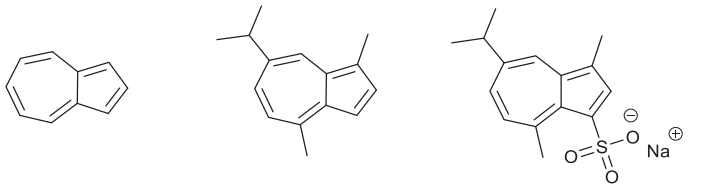


Figure 16 Azulene, the natural azulene derivative guaiazulene and its 3-sulfonate.

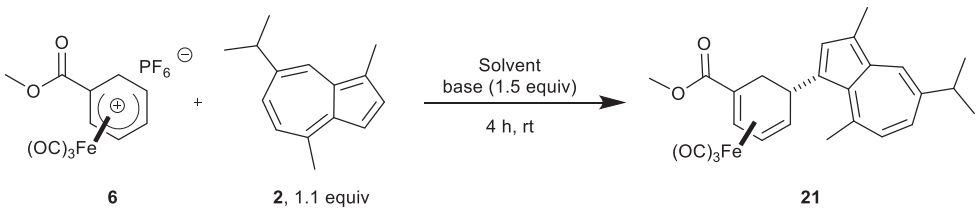
With the many promising areas of application of azulenes, new methods for their functionalization are of great interest. If azulenes could be alkylated using cationic iron carbonyl dienyl complexes, it would likely be an interesting addition to the currently available toolkit for azulene modification.

4.2.1 Optimization of the reaction conditions

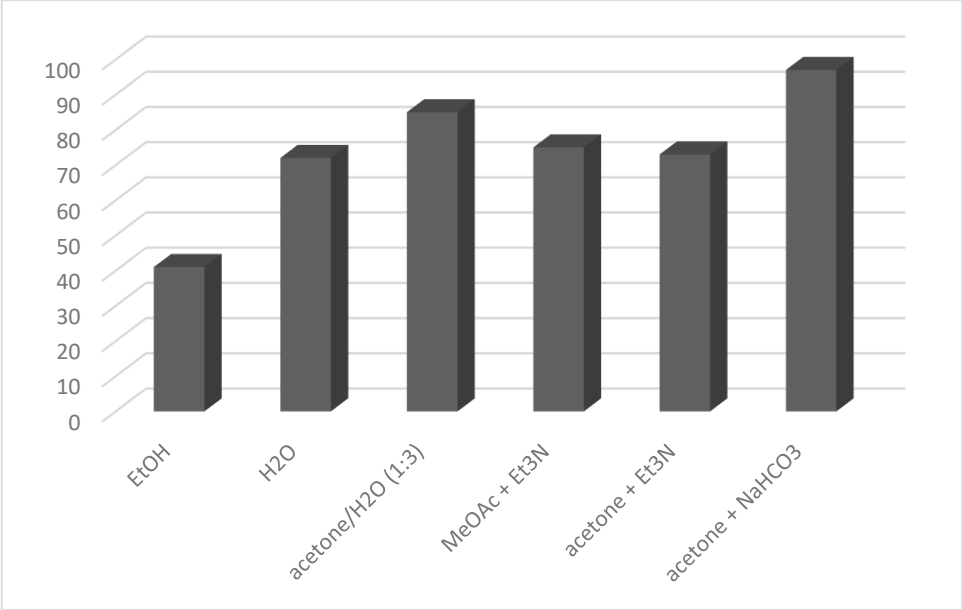
Initial tests using the optimized conditions from the *C*-addition of phenolic nucleophiles to cationic iron carbonyl complex **6** (ethanol as solvent, no base) showed that guaiazulene can indeed function as a nucleophile in this type of reaction, forming addition product **21**.

The yield after a reaction time of 4 hours was a modest 41%, however, and unreacted iron complex was filtered off at the end of the reaction. Changing to water as the solvent increased the yield to 72%. In this reaction, a heterogeneous mixture was formed, as neither guaiazulene, iron complex **6** or the formed product **21** is soluble in water. Mixing water and acetone increased the solubility of the reactants and improved the yield to 85%. Attempting to further increase the yield, a soluble base in the form of triethylamine was added in non-protic solvents (to avoid solvent addition), affording the product in 75% and 73% in acetone and methyl acetate respectively.

*Table 2 Results from the solvent screening for the addition of guaiazulene to cationic complex **6**; yields quantified by NMR using p-xylene as internal standard.*



6 **2**, 1.1 equiv **21**



When a heterogenous base in the form of sodium bicarbonate was used together with acetone, **21** was obtained in 97% yield. As a nearly quantitative yield was obtained using inexpensive, green and benign chemicals, we were satisfied with these reaction conditions and proceeded to investigate the scope of the reaction.

4.2.2 Synthesis of azulene nucleophiles

Our next step was to evaluate the reaction using a range of azulene derivatives. We decided to approach the nucleophile scope from two directions: 1) employing azulenes derived from bio-derivable guaiazulene, and 2) using azulenes derived from the parent azulene, or other synthetic azulenes, with a focus on extending the azulene π-system.

In terms of guaiazulene-derived nucleophiles, we aimed at a small collection of azulenes containing both electron donating and electron withdrawing substituents. We also wanted to include a few guaiazulenes substituted with functional handles, which could be useful for further derivatizations of the azulene skeleton. The guaiazulenes used are shown in Figure 17. Boronic acid ester (**22**),[224] bromide (**23**),[224] iodide (**24**),[224] 2-*p*-tolyl azulene (**25**)[225] and aldehyde **26**[226] were synthesized according to reported literature procedures. The haloazulenes as well as the boronic ester provide synthetic handles which could be useful for instance in cross-coupling reactions. The carbaldehyde-functionalized guaiazulene **26** serves as an electron deficient substrate.

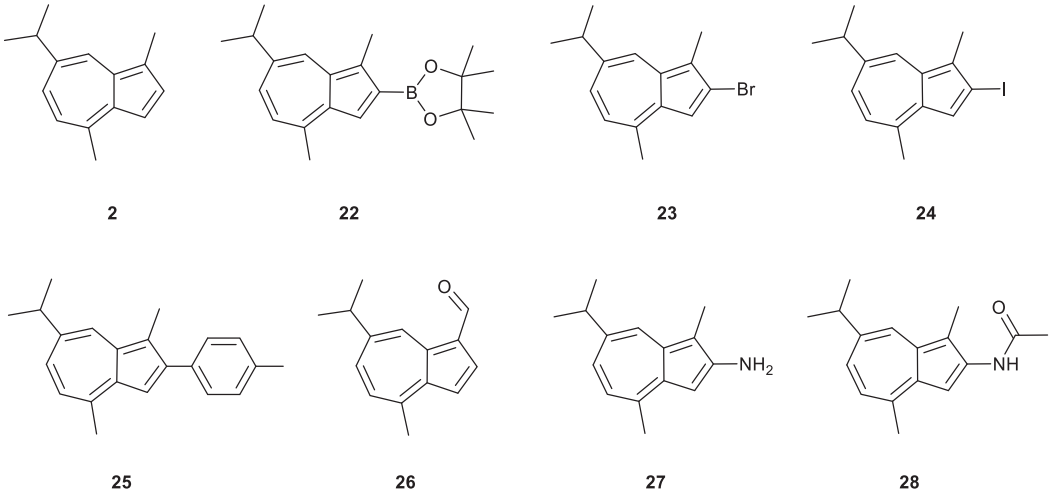
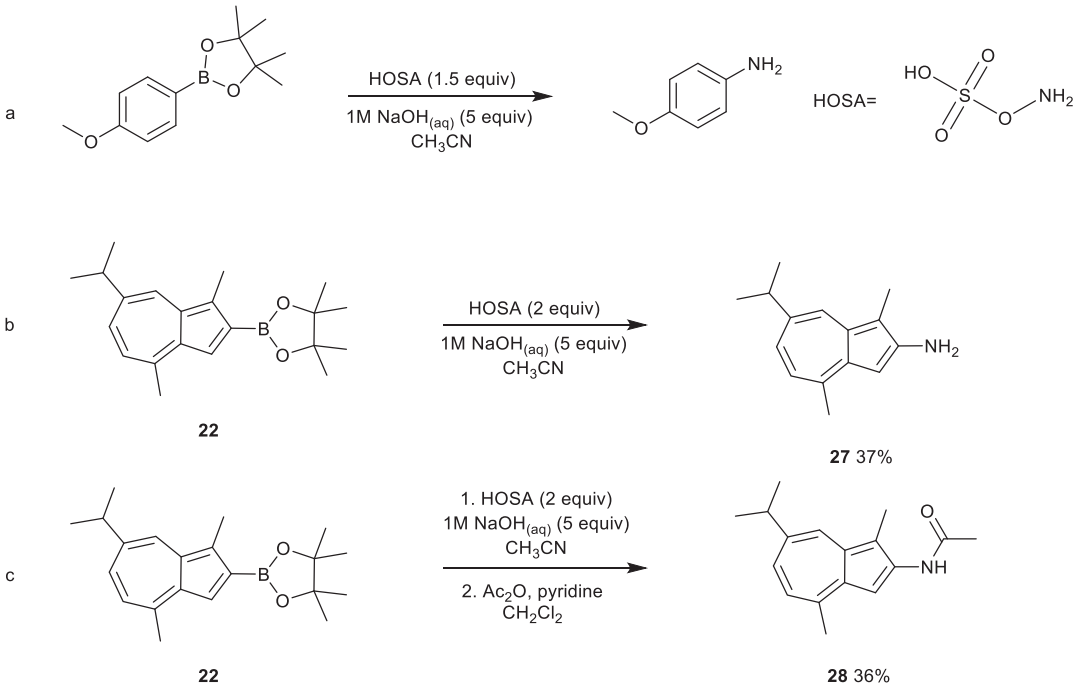


Figure 17 Scope of guaiazulene-based nucleophiles for the addition to cationic iron carbonyl diene complexes.

For the synthesis of electron rich 2-aminoguaiazulene **27**, we turned to a method reported by McCubbin for the synthesis of anilines from aryl boronic acids and boronic acid esters using hydroxylamine-*O*-sulfonic acid (HOSA) (Scheme 35).[227] Although this transformation has been used for a range of aromatic and heteroaromatic substrates, there was no previous report of its use to synthesize an aminoazulene.



Scheme 35 ***a****: Amination of aryl boronic acid ester reported by McCubbin.* ***b****: Synthesis of 2-aminoguaiazulene* ***27****.* ***c****: Synthesis of acylated 2-aminoguaiazulene* ***28****.*[227]

Initial attempts were successful, but with a disappointing yield of 28%. We found that by increasing the amount of HOSA to 2 equivalents, the yield could be improved somewhat to 37%.

Further increasing the excess of HOSA did not improve the results. Acetamide-functionalized guaiazulene **28** was prepared by acylation of the crude aminoazulene **27**.

Other than the guaiazulene-derived nucleophilic scope and azulene itself, a number of azulenes with an extended π-system were synthesized (Figure 18). 6-Phenylazulene **29** was prepared by a Ziegler-Hafner synthesis,[228] and azulene-1-carbaldehyde **30** was obtained via a Vilsmeier-Haack formylation of azulene.[229] Azulenes **31**-**33** were formed using cross-coupling reactions with an azulenesulfonium salt.[230] 1-Phenylazulene **31** and 1-thienylazulene **32** were prepared using Suzuki reactions, and alkynyl-functionalized azulene **33** was obtained using a Sonogashira coupling.

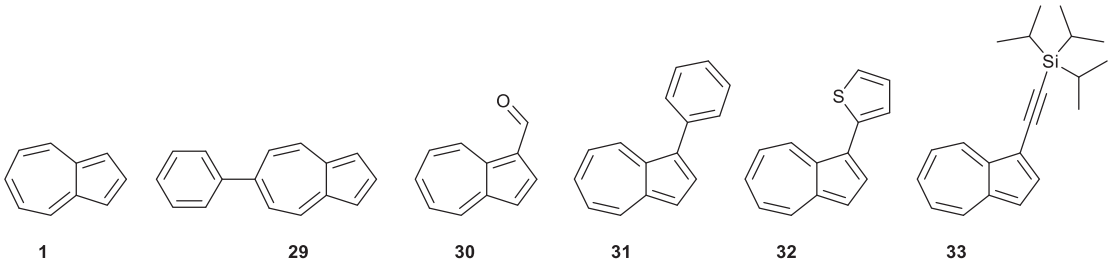


Figure 18 Scope of synthetic azulene derivatives for the addition to cationic iron carbonyl diene complexes.

4.2.3 Addition of azulene nucleophiles to cationic iron carbonyl complexes

The guaiazulene-based nucleophiles were evaluated using the optimized conditions from the initial screening. To compare their reactivity, electronically activated iron complex **6**, unsubstituted iron complex **34** and electronically deactivated iron complex **35** (Figure 19) were reacted with guaiazulene (Scheme 36).

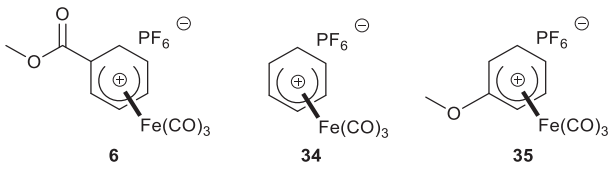
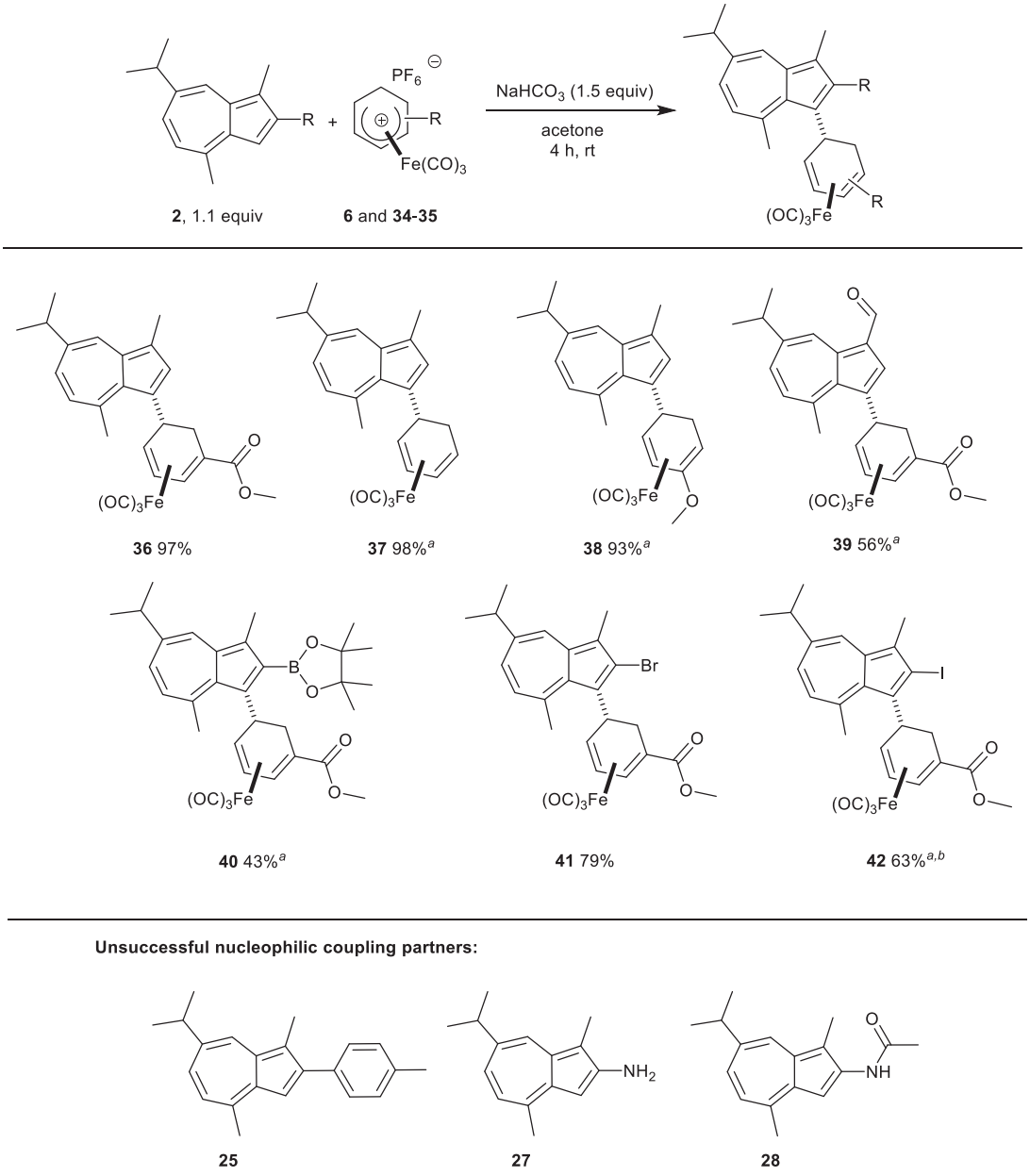


Figure 19 The three cationic iron carbonyl complexes used as electrophiles for the azulene additions.

Iron complex **6**, as expected, proved to be the most reactive, giving **36** in 97% yield after 4 hours. Addition to complex **34** also resulted in near quantitative yield but required an extended reaction time of 16 hours to reach full conversion. Methoxy-substituted cationic complex **35** was the least reactive, but still gave addition product **38** in a high yield of 93% after 16 hours.



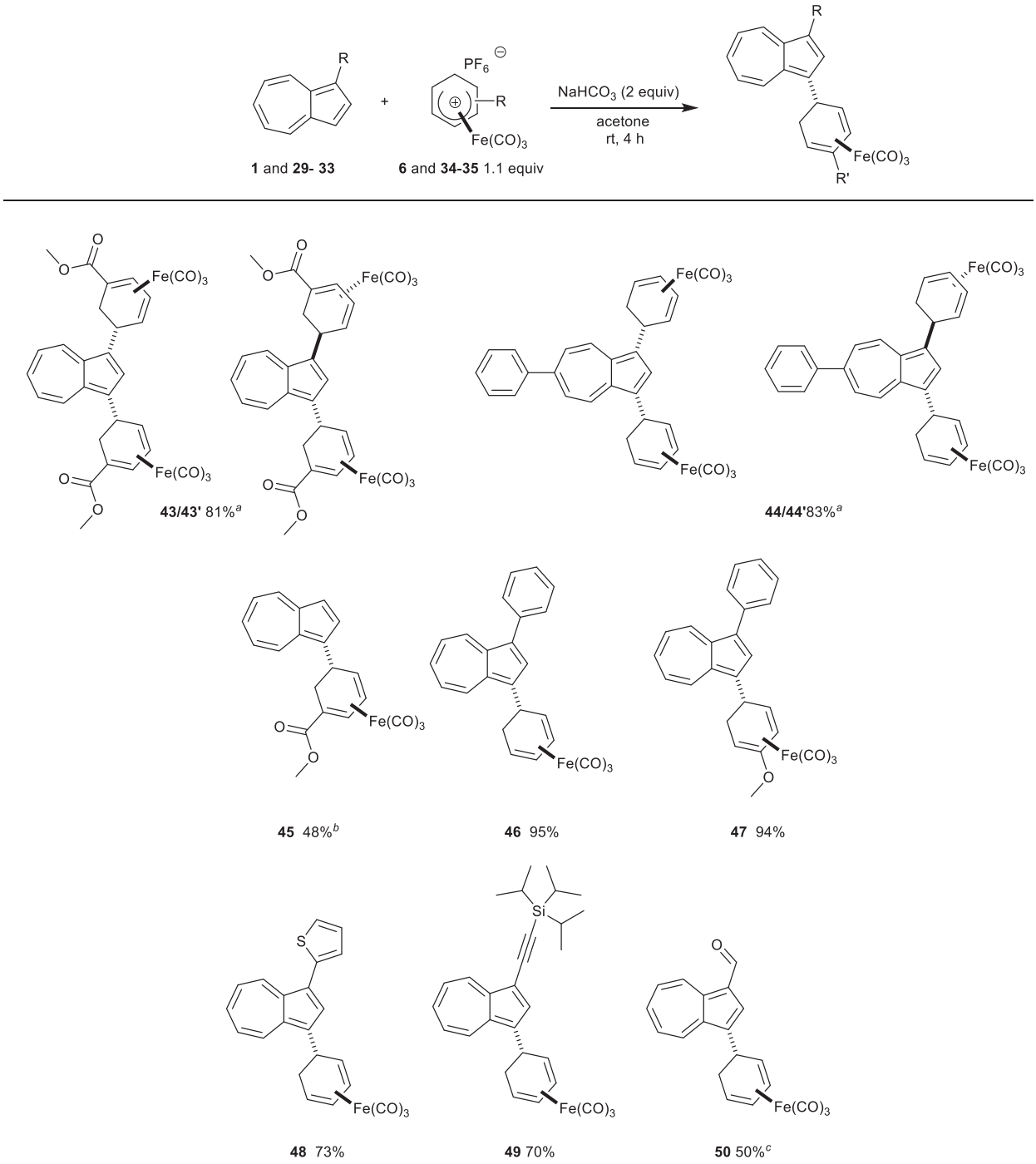
*Scheme 36 Results from the addition of guaiazulene-based nucleophiles to cationic complexes **6**, **34** and **35**; [a]16 h reaction time. [b]Excess of **2** (1.1 equiv).*

The guaiazulene derived nucleophiles **22**-**28** were then evaluated in the addition to the most reactive cationic iron complex **6**. The electron poor, formyl-functionalized guaiazulene **26**, not unexpectedly, reacted slower than guaiazulene itself, affording addition product **39** in 56% yield after 16 hours. The reaction proved to be somewhat sensitive towards substituents in the 2-position of the guaiazulene. Azulene **22**, functionalized with a boronic acid ester in the 2-position gave a moderate 43% yield after an extended reaction time. 2-Bromoguaiazulene (**23**) yielded addition product **41** in 79% yield after 4 hours, while 2-iodoguaiazulene (**24**) gave 63% yield of **42** after 16 hours reaction time using an excess of electrophile. The difference in reactivity between the two 2-haloguaiazulenes suggests that steric bulk might play a role in the lower reactivity of some 2-

substituted guaiazulenes. Attempted addition of 2-*p*-tolyl-substituted guaiazulene **25** failed altogether, and unreacted starting material could be recovered without any sign of addition. The 2-aminoguaiazulene **27** proved to be unstable under the reaction conditions, the starting material was fully degraded, but no addition products were observed. The instability of **27** under the reaction conditions, could be addressed in part by employing the acylated aminoguaiazulene **28**. However, while a coupling between **28** and iron complex **6** could be detected in the crude NMR spectrum, attempts to isolate the product only led to degradation. The identity of the product is not completely clear, and it is likely that a mixture of *C*- and *N*-addition product was formed.

The next step was to evaluate the scope of synthetic azulene derivatives. Azulene itself possesses two nucleophilic sites, therefore a mixture of mono- and disubstituted product is to be expected. In order to tailor the reaction conditions to higher selectivity, variation of the stoichiometry was used. By using an excess (2.2 equiv) of electrophile **6**, double addition product **43**/**43'** could be obtained in 81% yield as a 1:1 mixture of diastereomers (Scheme 37). In the same manner, by employing an excess of azulene (5 equiv), the monoaddition product **45** could be obtained in 48% yield, along with 30% yield of the double addition products **43**/**43'**. Similarly, 6-phenylazulene **29** also has two nucleophilic carbons. By employing the same conditions as in the double addition to azulene, addition of iron complex **34** proceeded in 83% yield, forming products **44/44'** as an equimolar mixture of diastereomers.

Azulene is significantly more expensive than guaiazulene. Therefore, the addition of azulene-derived nucleophiles possessing a single nucleophilic site were evaluated using an excess of iron complex, rather than an excess of nucleophile as for the guaiazulene based nucleophiles. The results are summarized in Scheme 37. Addition of 1-phenylazylene to iron complex **34** and **35** proceeded smoothly, yielding **46** and **47** in 95% and 94% yield respectively. Addition of 1-thienyl functionalized azulene **32** to unsubstituted iron complex **34** gave a yield of 73%. Thiophenes are also competent nucleophiles in these types of reactions, so competing double addition could be a potential outcome. However, thiophenes have a relatively low reactivity,[141] and no double addition product could be identified. Alkenyl-substituted azulene **33** could be added in a good yield of 70%, while the more electron deficient azulene 1-carbaldehyde formed addition product **50** in 50% yield.

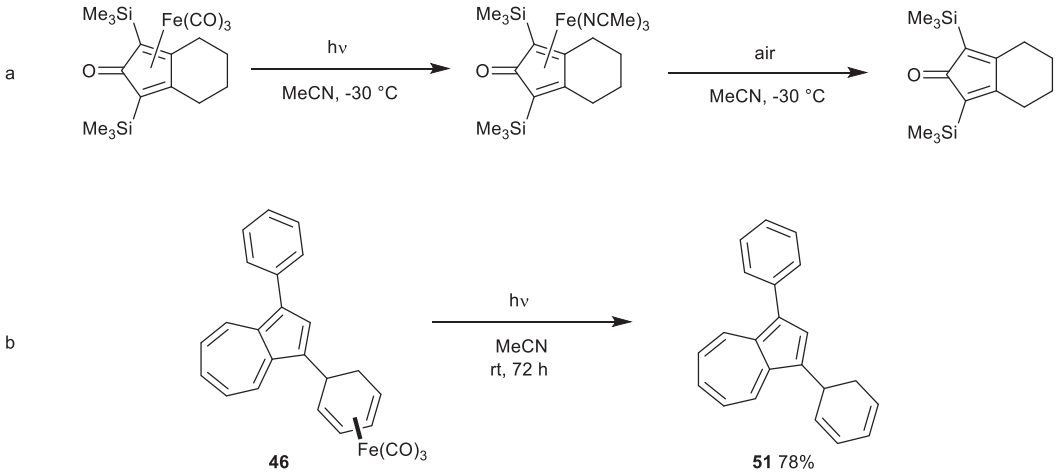


Scheme 37 Results from the addition of synthetic azulene derivatives. [a]2.2 equiv electrophile, 4 equiv $NaHCO_3$. [b]5 equiv nucleophile. [c]16 h reaction time.

4.2.4 Demetallation and further functionalization of addition products

To make this azulene functionalization method more attractive and versatile for further organic synthesis, we wanted to demonstrate a method for the removal of the iron moiety from the addition products. Many of the commonly used methods for oxidative iron decomplexation of these types of products (basic hydrogen peroxide, trimethylamine *N*-oxide, cupric chloride and cerium

ammonium nitrate were tried) were found to be too harsh, resulting in partial, or full decomposition of the starting material. Instead, we turned to a photolytic demetallation strategy developed by Knölker[231] for the decomplexation of oxidatively sensitive iron carbonyl diene complexes (Scheme 38).



Scheme 38 a: Mild photolytic demetallation of oxidatively sensitive substrate developed by Knölker. b: Conditions used for the demetallation of azulene addition products.

Knölker's method relies on photolytic ligand exchange at -30 °C followed by oxidation by air (Scheme 38, a). We were able to use a simpler method, where an acetonitrile solution of the iron complex was irradiated by UV-light at room temperature, in a vessel open to the atmosphere (Scheme 38, b). The demetallation could be carried out without the need for specialized equipment using a low energy blacklight light bulb. With this setup, the demetallation of iron complex **46** proceeded over 72 hours, producing compound **51** in 78% yield (Scheme 38). It is likely that the reaction time could be significantly shortened by using a more powerful light source. Upon demetallation of addition products of the 2-methoxy substituted iron complex **47**, as well as **38**, 2,3-cyclohexenones **52** and **53** were obtained as the products rather than enol ethers (Figure 20). This is a known type of reactivity,[146,232] and gives access to yet another class of functionalized azulenes.

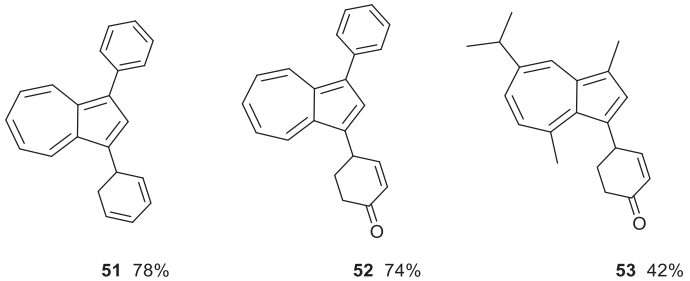
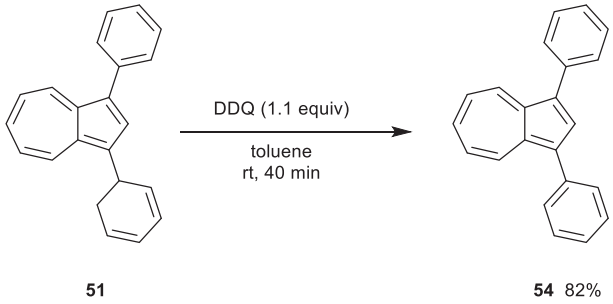


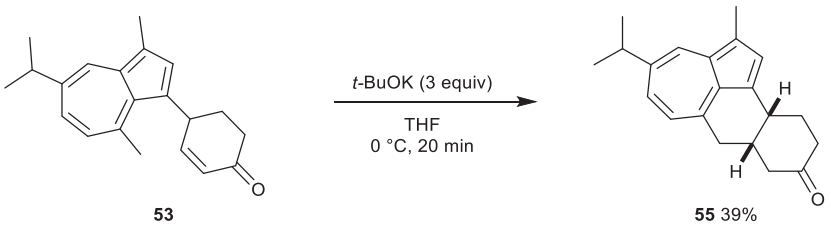
Figure 20 Demetallated azulene addition products.

The cyclohexadiene-functionalized azulene **51** could be dehydrogenated by oxidation with DDQ (Scheme 39). Diphenylazulene was obtained in good yield, demonstrating that this method can be used for azulene arylation.



Scheme 39 Aromatization of a demetallated azulene addition product by DDQ oxidation.

The protons on the C-4 methyl group of guaiazulene are acidic, as the anion formed upon deprotonation is stabilized by hyperconjugation with the electron poor seven membered ring. This has been utilized, for example in the synthesis of various chromophoric materials by condensation of the C-4 methyl group and aromatic aldehydes under basic conditions.[88] There are also some limited examples of base-mediated conjugate additions to guaiazulene.[233] The demetallated guaiazulene addition product **53** possesses an unsaturated ketone moiety, which could be well set up for an intramolecular conjugate addition from the C-4 methyl group. Upon exposing compound **53** to potassium *tert*-butoxide in THF, tetracyclic azulene derivative **55** was formed as a single diastereomer (Scheme 40). The *cis*-fused structure of the ring system was determined by the observation of a strong NOE between the two ring-junction protons.



*Scheme 40 Intramolecular cyclization of demetallated guaiazulene addition product **53**.*

4.2.5 Spectroscopic investigations

In addition to the vivid visible colors, azulenes are known for showing halochromic properties i.e. to undergo color changes upon protonation,[86,88,234] and many azulenes also display a fluorescence turn-on response, induced by protonation.[235] Furthermore, iron carbonyl-diene moieties display strong, characteristic vibrational absorption bands.[236] In order to increase the interest for our formed products for potential application such as multimodal chemical sensing, their spectroscopic properties were investigated. Azulenes **43**/**43'**, **47**, **37**, **51** and **52** were assessed for their halochromic responses to trifluoroacetic acid (TFA). Exposure to a large excess of TFA resulted in color changes, clearly visible to the naked eye. All the investigated azulenes also showed a significant fluorescence turn-on response upon exposure to TFA, proving that functionalization with tricarbonyliron-diene in the 1-, and/or 3-position does not quench the fluorescence of azulenes. Interestingly, the azulene addition product which showed the greatest fluorescence was the doubly functionalized azulenes **43/43'**. As expected, all azulenes possessing tricarbonyliron-diene substituents exhibited strong IR-absorption peaks in the 2100-1900 cm^{-1} region. This is a

window where most biological media are transparent,[198,236] opening up for potential applications as bioprobes.[237,238]

4.2.6 Summary and outlook

A new method for azulene alkylation has been demonstrated, using electrophilic cationic η^5 iron carbonyl dienyl complexes. The azulene additions proceeded smoothly under green reaction conditions, at room temperature in acetone solvent, with inexpensive and benign sodium bicarbonate as the only additive. Naturally derived guaiazulene could be coupled in excellent yields to three different iron complexes of varying electronic activation. The scope of the reaction was further examined using seven functionalized azulenes synthesized from natural guaiazulene. The reaction was found to be somewhat sensitive towards substitution in the 2-position of the guaiazulene skeleton. Five azulene derivatives possessing extended conjugated systems could be functionalized in good to excellent yields. Azulene itself, possessing two nucleophilic sites could be selectively mono- or dialkylated by variation of the reaction stoichiometry. Guaiazulene could also be alkylated by an electrophile formed in situ from a neutral tricarbonyliron diene complex and tetrafluoroboric acid.

Demetallation of the addition products was demonstrated to make them more interesting for synthetic applications. The products were sensitive to many of the strongly oxidative demetallation procedures that are commonly used. They could, however, be demetallated in good yields using a mild, photolytic procedure with air as the oxidant, liberating either the free diene or a conjugated ketone, depending on the substitution pattern on the cyclohexadiene scaffold. The free diene could in turn be aromatized by DDQ oxidation. Lastly, a demetallated guaiazulene addition product could be converted to an interesting tetracyclic compound by an intramolecular base-catalyzed conjugate addition.

Spectroscopic investigations were conducted on some of the formed products. All investigated azulenes showed halochromic properties, changing color upon exposure to acid. In addition, the azulenes also displayed a fluorescence turn-on response

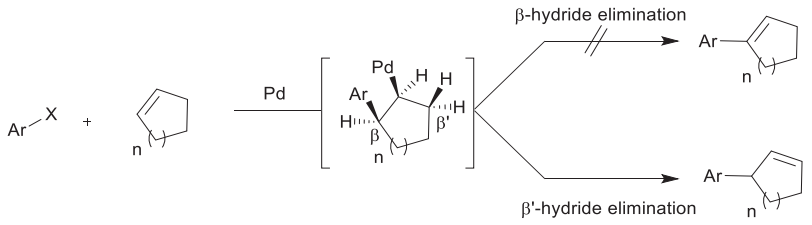
The presented method gives access to new classes of azulene derivatives, which would be difficult to obtain by other means. The method thus has the potential to be a valuable addition to the toolbox available for synthetic azulene chemistry. The spectroscopic properties of the formed addition products could prove useful, and in combination with the characteristic IR-absorption peak of the tricarbonyliron moiety, makes these products interesting candidates for multimodal sensing applications.

5 Heck-type functionalizations of microbial arene oxidation products

Benzoic acid dihydroxylating dearomatization using benzoic acid dioxygenase (BZDO) is a convenient way to obtain a chiral, highly functionalized molecule (**4**) from a simple, inexpensive precursor. Benzoic acid is a natural product, present in many fruits,[239] where lingonberry juice has been reported to contain concentrations of 0.7 g/L.[240] While lingonberries are not a convenient commercial source of benzoic acid, methods to produce benzoic acid via fermentation of glucose[241] or from glucose fermentation products,[242,243] as well as from lignocellulosic biomass[244] have been developed, providing a potential renewable source for this platform chemical. Despite their unique configuration, *ipso, ortho* diol microbial arene oxidation (MAO) products such as **4** (Scheme 41) have been underutilized for synthetic applications, compared to the products formed via microbial *ortho, meta* dihydroxylation of arenes.[245] We therefore wanted to explore selective functionalizations on a *ipso, ortho*-dihydroxylated MAO product, to produce novel enantiopure products of high synthetic utility. The Heck reaction is a versatile tool for functionalization of unsaturated substrates and has found wide synthetic application.[152] However, to our knowledge, the reactivity of *ipso, ortho*-dihydroxylated MAO products in Heck-type reactions has not been studied.

Scheme 41 Microbial ipso, ortho dearomatizing dihydroxylation of benzoic acid.

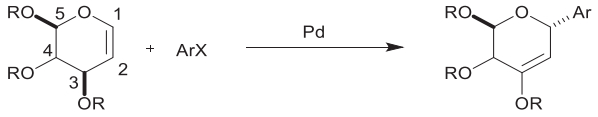
Endocyclic alkenes show a special selectivity in the Heck reaction. As both the carbopalladation and the β-hydride elimination are *syn*-processes, a C-C bond rotation is necessary in order to yield the usually favored conjugated products. When an endocyclic alkene is used, this rotation is not possible, and a β'-hydride elimination occurs instead (Scheme 42).[163] This selectivity has been exploited in asymmetric Heck reactions[164] and can for example be used to form quaternary chiral centers.[246]



Scheme 42 Heck reactions on endocyclic alkenes leads to non-conjugated products.[163,164]

One case where this stereoselectivity is well known is in the synthesis of *C*-glycosides from glycals (Scheme 43).[247] In this case, only one β-hydrogen is available for abstraction. Elimination of this hydrogen will result in a double bond migration and the *syn*-requirement of the carbopalladation

and β-hydride elimination will afford a chirality transfer from C-3 to C-1. It has been shown that the stereoselectivity of the arylation depends only on the configuration at C-3.[248] The high selectivity of these transformations could be caused by a reversibility in the carbopalladation step, but this has not been proven.

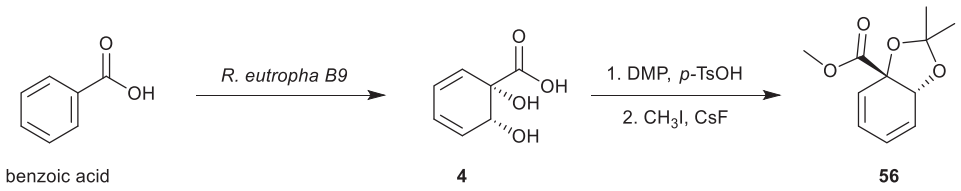


Scheme 43 Chirality transfer from C-3 to C-1 in the synthesis of a C*-glycoside by Heck arylation of a glycal.*[247]

After the alkene insertion step in a Heck-reaction, the formed alkyl palladium intermediate is highly reactive. If no *syn* β-hydrogen is accessible, or if there is another more favorable reaction path available, this intermediate can be further functionalized in a domino reaction. Many palladium-catalyzed coupling reactions, such as the Suzuki, Sonogashira or Negishi reactions, work well to terminate a domino reaction, as palladium is expelled in the C-C bond forming step. The Heck reaction, however, also offers a convenient way to initiate a palladium-catalyzed cascade reaction, as the C-C bond forming step creates this reactive organopalladium intermediate. A variety of Heck-type carbopalladation-initiated domino reactions have been demonstrated,[249,250] such as C-H activations, nucleophilic trapping, and carbonylations. As these types of domino reactions are often able to build up a high degree of complexity in a single synthetic step, development of new types of palladium-catalyzed domino reactions are of great interest.

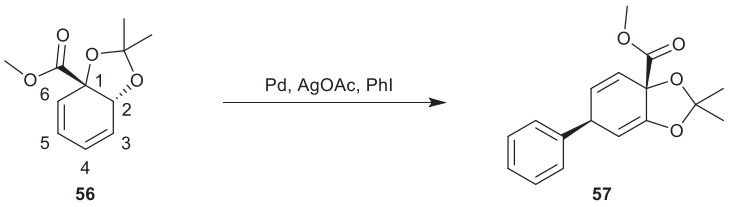
5.1 Heck-type arylation of microbial arene oxidation products (Paper III)

At the onset of our investigation we set out to achieve diversification of *ipso, ortho*-cis diol **5**, obtained by oxidation of benzoic acid by BZDO expressing *Ralstonia eutropha* B9 (Scheme 44). The acetal-protected methyl ester **56** was chosen as a model substrate owing to its ease of access from the bioproduct **4** and relatively high stability compared to the free carboxylic acid diol.



Scheme 44 Synthesis of ***56*** *from MAO product* ***4****.*

Upon subjecting **56** to a set of palladium-catalyzed arylating conditions, using aryl iodide together with excess silver acetate as a halide scavenger, we discovered the formation of **57**. The product was obtained in a low yield, but with high selectivity and as a single diastereomer. It was rationalized that this product would arise from a Heck-type mechanism, by arylation at C-4 followed by elimination of the only available β-hydrogen in a *syn* configuration at C-5 (Scheme 45). As in the glycal arylations, the reaction results in a chirality transfer from C-2 to C-4.

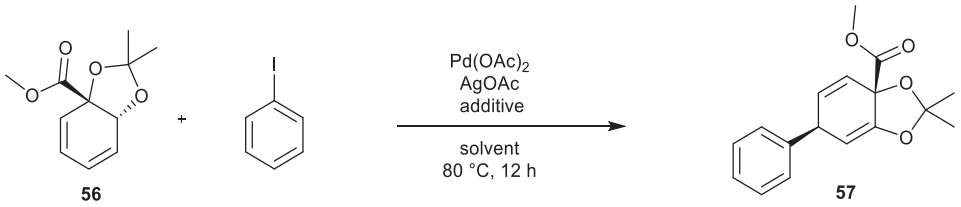


*Scheme 45 Heck-type arylation of MAO-derivative **56**.*

5.1.1 Reaction optimization

Encouraged by these initial results, we performed an optimization of the reaction conditions in order to maximize the yield of the arylated product **57**. The reactions were conducted in a Radleys Carousel Reaction Station™ equipped with a cooled reflux head, at 100 °C for 12 hours. Yields were evaluated using quantitative NMR with DMF as an internal standard. A summary of the results from the optimization can be found in Table 3.

Table 3 Reaction optimization.



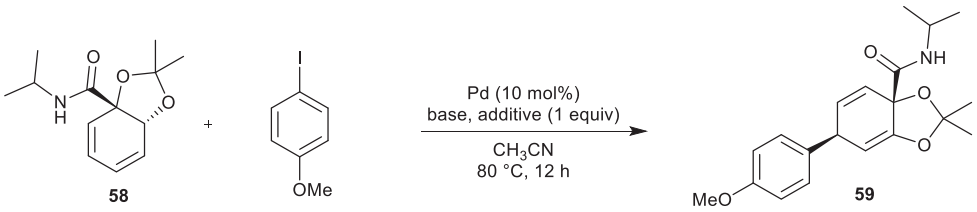
Entry	$Pd(OAc)_2$	Solvent	AgOAc	Additive	NMR yield (%)
1	10 mol%	toluene	2 equiv	-	35
2	10 mol%	THF	2 equiv	-	40
3	10 mol%	dioxane	2 equiv	-	31
4	10 mol%	DCE	2 equiv	-	28
5	10 mol%	none	2 equiv	-	40
6	10 mol%	CH_3CN	2 equiv	-	60
7	20 mol%	CH_3CN	2 equiv	-	54
8	5 mol%	CH_3CN	2 equiv	-	43
9	-	CH_3CN	2 equiv	-	0
10	10 mol%	CH_3CN	2 equiv	PPh_3 (20 mol%)	70
11	10 mol%	CH_3CN	1.4 equiv	$P(C_6F_5)_3$ (20 mol%)	10
12	10 mol%	CH_3CN	1.4 equiv	PCy_3 (20 mol%)	20
13	10 mol%	CH_3CN	1.4 equiv	dppe (10 mol%)	70
14	10 mol%	CH_3CN	1.4 equiv	dppp (10 mol%)	26
15	10 mol%	CH_3CN	1.4 equiv	$P(OEt)_3$ (20 mol%)	64
16	5 mol%	CH_3CN	1.4 equiv	$P((4\text{-}CF_3)C_6H_4)_3$ (10 mol%)	80
17	2.5 mol%	CH_3CN	1.4 equiv	$P((4\text{-}CF_3)C_6H_4)_3$ (5 mol%)	72

Initial screening identified acetonitrile as the best solvent (entries 1-6), producing the arylated product **57** in 60% yield, while driving the reaction to full conversion. Reducing the catalyst loading to 5% resulted in incomplete conversion, while an increase to 20% provided no improvement (entry 7 and 8). Conducting the reaction without catalyst resulted in close to full return of the starting material (entry 10). It was found that the addition of phosphine ligands could improve the yield and a ligand screening identified P(*p*-$(CF_3)C_6H_4)_3$ as the best option, affording product **57** in 80% yield (entries 10-15). Using these new conditions, the catalyst loading could be reduced to 5% without any decrease in yield (entries 16-17).

It was also found that the reaction could be conducted under silver free conditions, using amine bases. As the use of excess silver is not ideal from both an environmental and economic point of view, large efforts were made in order to optimize the reactions using these conditions. A ligand free reaction using *N,N*-diisopropylethylamine (DIEA) as a base produced **57** in 34% yield, with incomplete conversion. Unfortunately, no better conditions were identified using methyl ester **56**.

A more extensive optimization of the silver free reaction was performed on the isopropylamide derivative **58**, which showed better results under these conditions. Several amines and inorganic bases were screened, and triethylamine resulted in the highest yields of arylated amide **59** (Table 4, entries 1-8).

*Table 4 Optimization for the Heck-arylation of **58** using silver free conditions.*



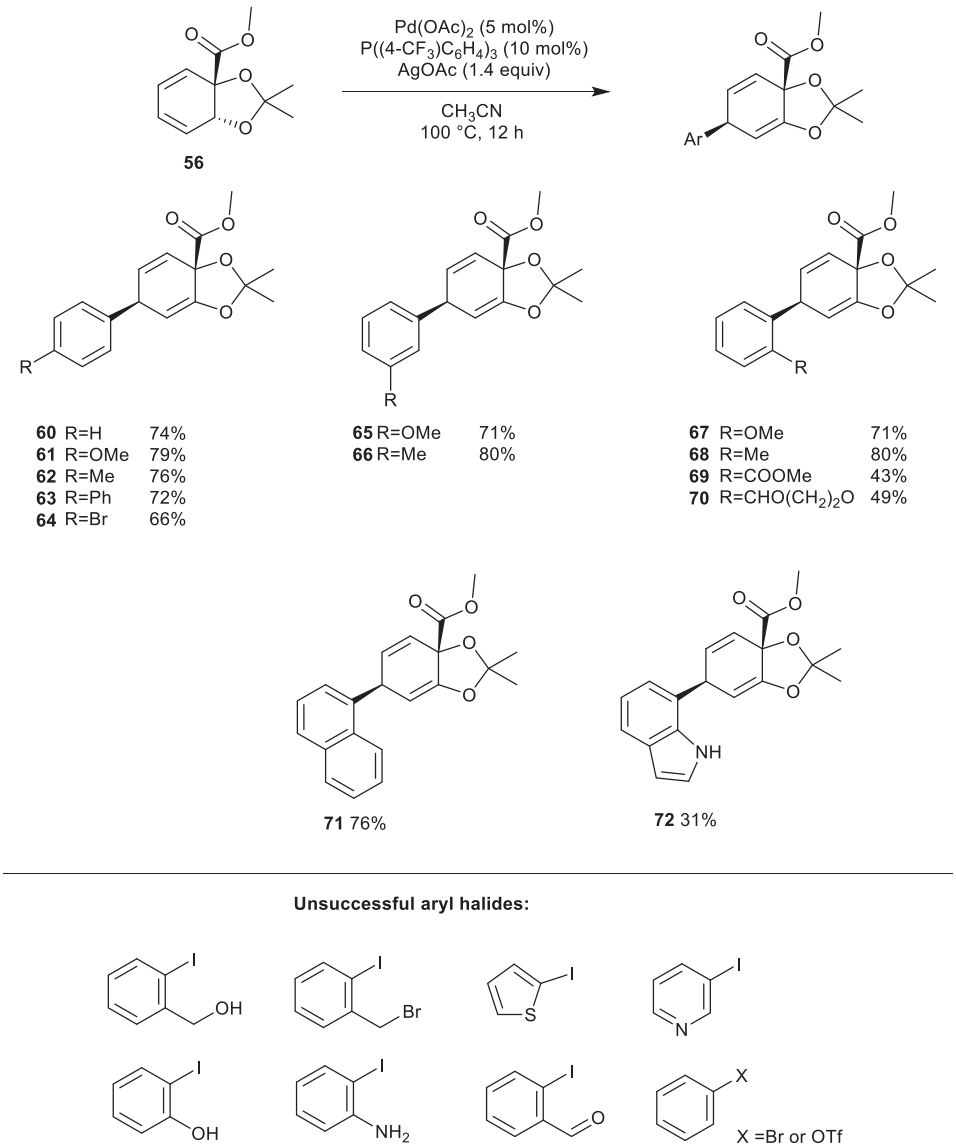
58 **59**

Entry	Catalyst	Additive	Base	NMR yield %
1	Pd/C	-	Et_3N (2 equiv)	52
2	Pd/C	-	DIEA (2 equiv)	26
3	Pd/C	-	proton sponge (2 equiv)	5
4	Pd/C	-	DBU (2 equiv)	0
5	Pd/C	-	K_3PO_4 (2 equiv)	0
6	Pd/C	-	pyridine (2 equiv)	6
7	Pd/C	-	NaOAc (2 equiv)	0
8	Pd/C	-	K_2CO_3 (2 equiv)	0
9	$Pd(OAc)_2$	TBAF	Et_3N (1.5 equiv)	0
10	$Pd(OAc)_2$	TBACl	Et_3N (1.5 equiv)	14
11	$Pd(OAc)_2$	TBABr	Et_3N (1.5 equiv)	40
12	$Pd(OAc)_2$	TBAI	Et_3N (1.5 equiv)	32
13	$Pd(OAc)_2$	TMABr	Et_3N (1.5 equiv)	63
14	$Pd(OAc)_2$	TMABr (2 equiv)	Et_3N (1.5 equiv)	60

The reaction worked with both $Pd(OAc)_2$, and Pd/C, producing similar yields around 50%. Attempts using the Jeffrey conditions,[158] with tetraalkylammonium halide salt additives, resulted in increased yields of up to 63% when using 1 equivalent of tetramethylammonium bromide (entry 13) but the reactions suffered from incomplete conversion, possibly due to catalyst deactivation. The fact that silver is needed in order to reach full conversion indicates that the desired reaction is promoted by abstraction of a halide ligand from palladium.

5.1.2 Reaction scope and limitations

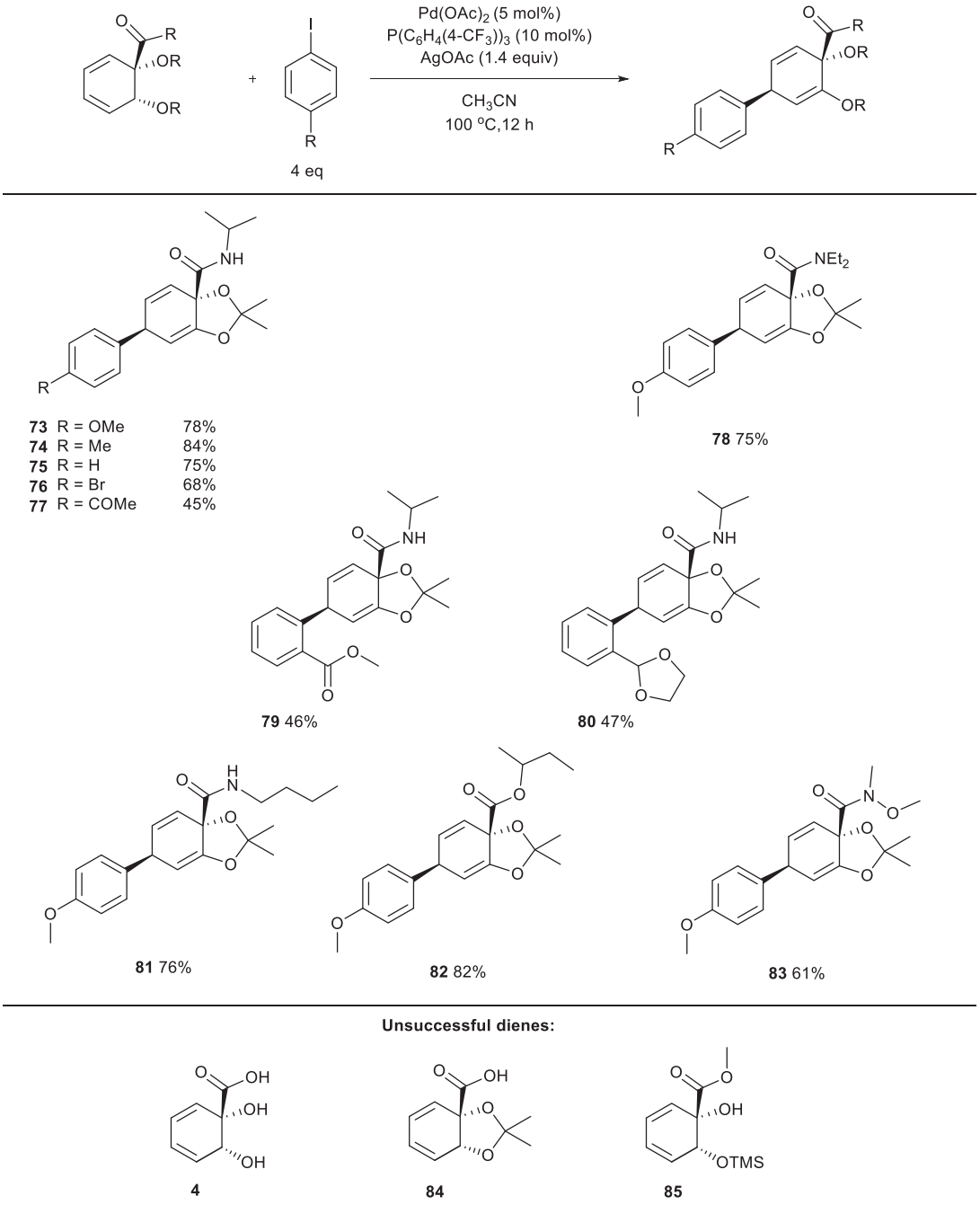
With the optimized conditions in hand, the scope of the transformation was investigated. The range of alkyl halides that could be used was evaluated using methyl ester **56** as the diene coupling partner. The results can be seen in Scheme 46.



Scheme 46 Aryl halide scope and limitations.

Aryl iodides possessing electron donating or electron neutral substituents in the *para* position performed well, yielding arylated 1,4-diene products in 70-80% yield. Electron poor aryl iodides performed modestly, although still yielding the desired product. The reaction was also tolerant to substituents in the *meta* and *ortho* positions. As a general trend, electron withdrawing substituents also produced lower yields. Functional groups that were not tolerated in the *ortho* position include aldehyde, phenol and aniline. Some polycyclic aromatic iodides could also be used. 1-Iodonaphthalene performed well, forming **71** in good yield and *N*-heterocyclic 7-iodoindole yielded the desired arylated product **72**, although in quite low yield. Other tested heteroaromatic iodides did not work under these conditions. Only aryl iodides were successful in this reaction, aryl bromides and triflates were tested but no conversion of the starting material was seen.

The next step was to investigate the scope of the diene coupling partner. Due to the limited substrate compatibility of the biotransformation, we decided to use the carboxylic acid and diol as synthetic handles by which we could vary the starting material. Primary and secondary amides and esters performed well (Scheme 47). A Weinreb amide could also be used as a competent coupling partner, producing **83** in moderate yield and providing a potentially useful synthetic handle for further functionalizations.

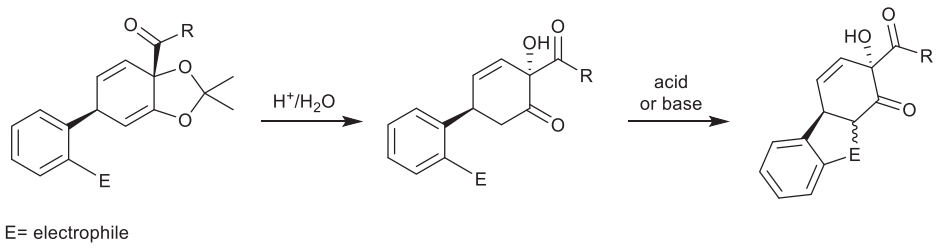


Scheme 47 Scope and limitations of the diene coupling partner.

Both the unmodified MAO-product **4** and the acetal protected free acid **84** were completely degraded under the reaction conditions. Attempts to arylate the methyl ester **85**, where the secondary alcohol had been protected as a trimethylsilyl ether, were unsuccessful, resulting in incomplete conversion of the starting material.

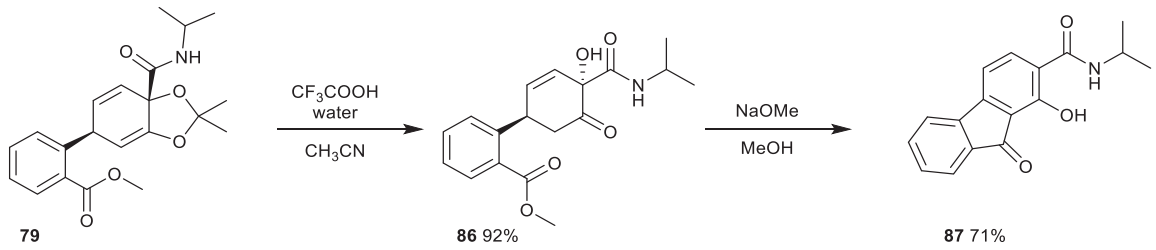
5.1.3 Further derivatizations

We wanted to explore the possibility to further derivatize the formed product, using the installed complexity for selective transformations. The arylation reaction produces enol ethers, which can be seen as masked enolizable ketones. If a compatible electrophile is present in the ortho position of the aryl ring, the system could be well set up for an intramolecular cyclization (Scheme 48).



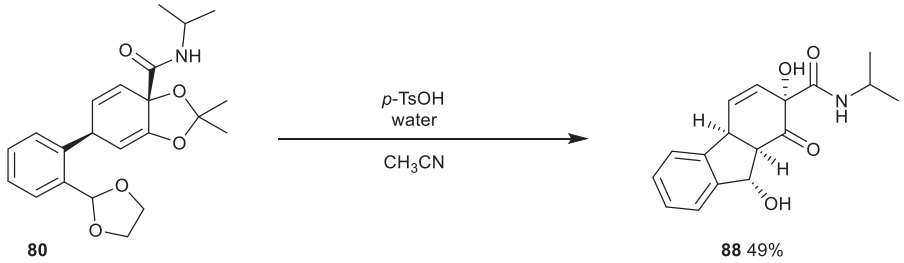
Scheme 48 Strategy for post-Heck cyclization.

Our first attempt at a cyclization was a Claisen condensation of the acetal-deprotected arylation product **86**, possessing a methyl ester in the 2-position of the aromatic ring. Acetal deprotection could be achieved in good yield using trifluoracetic acid in wet acetonitrile (Scheme 49). Treatment of the formed ketone with sodium methoxide did afford the desired cyclization, but yielded the aromatized fluorenone **87**, likely due to a subsequent dehydration of the condensation product, and thus all stereochemical information present in the starting material was lost (Scheme 49).



*Scheme 49 Claisen-type condensation of acetal deprotected arylation product **79**.*

To avoid the harsh basic conditions which resulted in aromatization, an acid-catalyzed aldol-type cyclization was attempted instead, starting from arylation product **80** possessing a benzaldehyde protected as an ethylene glycol acetal, *ortho* to the arylation position. As the same acidic conditions which are used to hydrolyze acetal protecting groups can also catalyze aldol reactions, we hoped that a domino reaction could be triggered, where deprotection of the two acetals would be followed by an aldol cyclization. We were happy to see that the reaction was successful, and upon treatment with *p*-TsOH in wet acetonitrile, the tricycle **88** was obtained in 49% yield. The reaction introduces two new stereogenic centers, forming the product as a single diastereomer (Scheme 50).



*Scheme 50 Acid-catalyzed domino deprotection-cyclization of arylation product **80**.*

A strong NOE between the two ring junction protons was used to determine the relative stereochemistry of tricycle **88** as a *cis*-fused system.

5.1.4 DFT calculations

We were interested in the origin of the high selectivity of the arylation reaction. Given the presence of an asymmetrically substituted cyclic diene, arylation is, in principle, possible in eight different positions. However, only two products can be formed through a Heck-type mechanism: the observed C-4 arylation product **57**, as well as the product **89** (Figure 21), formed via arylation at C-6 followed by palladium migration through a π-allyl system and subsequent β-hydride elimination.[168] The arylation (migratory insertion) step in a Heck-reaction is usually seen as being irreversible, but we were curious to see if arylation could also occur in other positions, but in a reversible manner. The formation of **57**, in the absence of phosphine ligands, was chosen as a model system for our calculations. The experimental reaction used silver acetate in acetonitrile solvent, so a fast halide abstraction from palladium after the oxidative addition was assumed, and all structures were modelled using acetate and acetonitrile ligands.

The selectivity-determining step in a Heck-reaction is the migratory insertion (carbopalladation).[152] This step generally operates under Curtin-Hammett control[251,252] and sometimes follows a Halpern-type selectivity, where the lowest energy transition state arises from a thermodynamically disfavored intermediate.[252–254] Therefore, we performed an extensive screening of migratory insertion transition states. The lowest energy transition state structures that were identified all contained one acetonitrile and one monodentate acetate coordinated to palladium.

The structures of the eight possible arylation transition states (**TS1-TS8**) are shown in Figure 21. The most favorable migratory insertion, **TS1**, leads to arylation in the C-4 position, on the same face of the ring as the carbonyl moiety (Figure 22). With an almost fully formed bond between palladium and the alkene carbon, along with a developing C-C bond, it resembles migratory insertion transition states previously reported in Heck reactions.[152,252,254] Our calculations predict that **TS1** is favored by 1.8 kcal/mol over the second lowest energy arylation, **TS2** (Figure 21). The results agree well with our experimental results, in which **57**, the product state following **TS1**, is the only observed Heck-product.

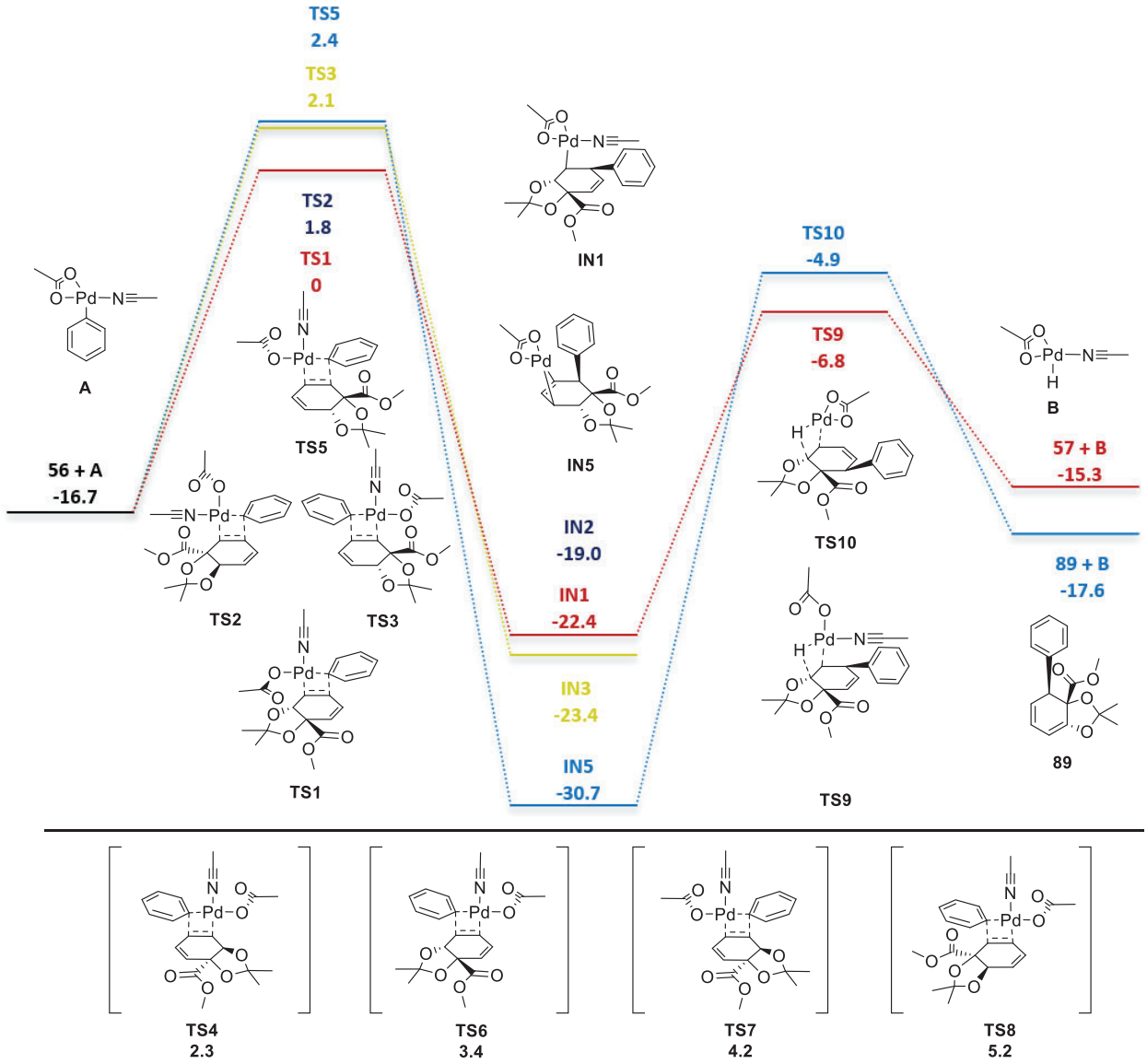


*Figure 21 Top: Gibbs energy profile (1M, 298K, in kcal/mol) for four of the migratory insertion transition states. Single point energies are calculated at the B3LYP-D3/def2-TZVP level of theory. The geometry of **TS1** is shown in Figure 22. Bottom: Transition state structures for four migratory insertions of higher energy. All energies are shown relative to **TS1**.*

In addition to **TS2**, there are other transition states near in energy to **TS1** that might contribute under our experimental conditions. These are **TS3**, predicted to lie 2.1 kcal/mol above **TS1**, as well as **TS4** and **TS5**, higher by 2.3 and 2.4 kcal/mol respectively. The insertion products following **TS2** and **TS3** have no available β-hydrogens and can therefore not proceed to form a Heck-type product. In absence of β-hydrogens, a reverse carbopalladation is possible. The migratory insertion in a Heck-type reaction is generally viewed as irreversible,[152,252,254–256] but there are examples of alkene extrusion when no β-hydrogens are available.[166,167] We have estimated the reaction barriers for reverse migratory insertion through **TS2** and **TS3** to ~21 kcal/mol and ~26 kcal/mol,

respectively. The calculated barriers suggest that the reverse migratory insertions are accessible under our experimental conditions. Therefore, if they occur, these arylations could be reversible.

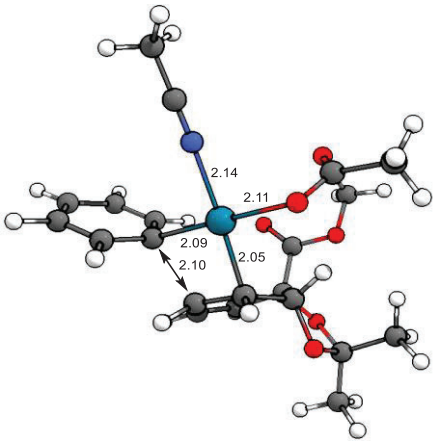


*Figure 22 Optimized structure for migratory insertion transition state **TS1**. Selected bond distances are shown in Ångström (Å).*

The migratory insertion product **IN1**, following **TS1**, possesses a hydrogen in a *syn* orientation with respect to the palladium. As expected, formation of this intermediate is predicted to be followed by a β-hydride elimination (**TS9**) (Figure 23) leading to product **57**. The barrier for this process was estimated to be 16 kcal/mol. This barrier is relatively high for a β-hydride elimination in a Heck reaction, which can be rationalized by the rigid conformation of the transition state. Significant distortion of the insertion product **IN1** is required for the palladium to reach the hydrogen in the equatorial β-position. Intermediate **IN5**, formed after arylation through **TS5** forms a π-allyl system. This results in a lower energy compared to the other insertion products, which have sp^3-bound palladium. However, **IN5** also has the potential to undergo a β-hydride elimination, where the available hydrogen at C2 can be accessed through palladium migration through the π-allyl system. While β-hydride elimination from π-allyl systems are known, they can be expected to be significantly slower than β-hydride eliminations from Pd-sp^3-carbon systems.[170] In accordance with this, the barrier for β-hydride elimination (**TS10**) (Figure 23) from **IN5** was calculated to be 26 kcal/mol. This barrier height implies that β-hydride elimination should be attainable under the experimental conditions, meaning that if formed, **IN5** could proceed to form Heck-product **89** (Figure 21).

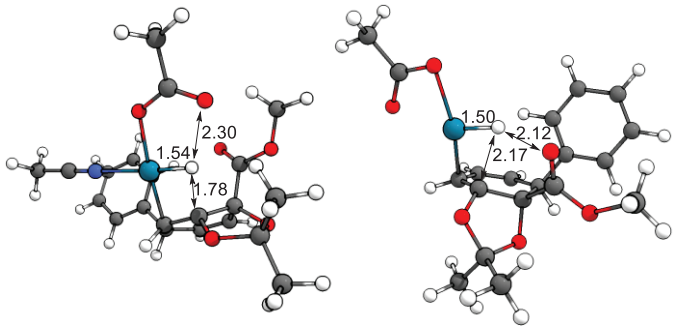


*Figure 23 Optimized structures for β-hydride elimination transition states **TS9** and **TS10**. Selected bond distances are shown in Ångström (Å).*

5.1.5 Summary and outlook

A selective Heck-type arylation of a range of highly functionalized cyclohexa-1,3-dienes derived from an *ipso*, *ortho* dihydroxylated microbial arene oxidation product of benzoic acid has been developed. The biocatalytic transformation and the palladium-catalyzed reaction shows an interesting synergy, introducing a high degree of complexity from simple flat aromatic starting materials in just a few synthetic steps. Furthermore, the transformation enables a 1,3-chirality transfer from the secondary alcohol to the newly formed C-C bond.

The reaction proceeds in good yields with several aryl iodides. The reaction also allows for some variations on the diene side of the scope in the form of different benzoic acid derivatives, amides and esters performed well, while the free acid did not work. Installation of a masked electrophile on the aryl halide allowed for a facile acid-catalyzed cyclization, forming a densely functionalized tricyclic product, demonstrating the synthetic utility of these types of molecules.

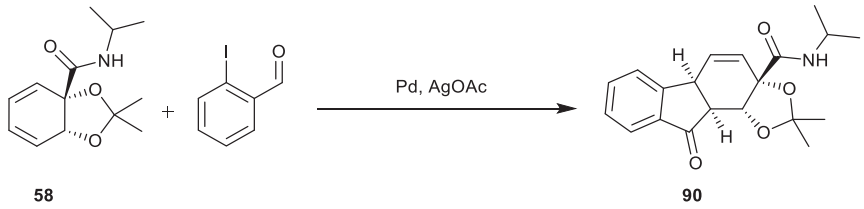
The optimized conditions employ phosphine ligands and silver acetate as an additive. In order to evaluate the possibility to perform the reaction under "greener" conditions, a silver and phosphine free alternative using an amine base was developed. These conditions however, resulted in incomplete conversion of the starting material and failed to produce the high yields seen using silver.

Similar products, with a 1,4-cyclohexadiene arylated at an sp^3-center, can be obtained for example by the addition of an organometallic reagent to a cyclohexadienone.[257] These highly functionalized chiral products however, obtained in a few steps from an inexpensive and readily available starting material, would most likely prove difficult to obtain by other synthetic routes.

The possible migratory insertions (the regio- and stereodetermining step) and β-hydride eliminations were modelled using DFT. This provides interesting insight into the mechanism of these types of reactions and shows that although the observed reaction is the kinetically favored path, reversible carbopalladations are potentially within reach under the reaction conditions.

5.2 Heck-type domino arylation-cyclization of microbial arene oxidation products (Paper IV)

During our investigation of the Heck-type arylation of MAO-products, we discovered the formation of an unknown product when 2-iodobensaldehyde was used in combination with diene **58**. Interestingly, the product was identified as the tetrahydrofluorenone **90** (Scheme 51). This indicates that a domino reaction has occurred, effecting an acylation after the initial arylation, forming the tricyclic product. The transformation creates two new C-C bonds and introduces two new stereocenters. Unlike our previously reported Heck-type arylation of the same class of MAO-products, all stereocenters present in the starting material are preserved.



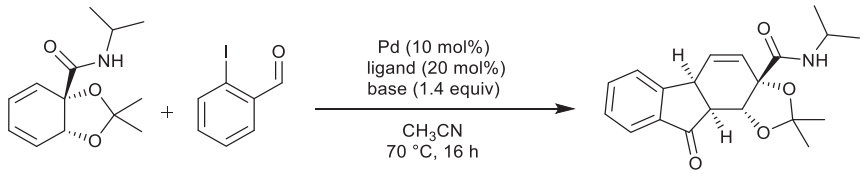
58 90

*Scheme 51 Cyclization reaction between MAO-product **58** and 2-iodobenzaldehyde.*

5.2.1 Reaction optimization

An extensive optimization of the reaction conditions followed; the results can be found in Table 5. As a starting point, we used the optimized conditions of the previously developed Heck arylation of MAO products, resulting in a yield of 66% in this case (entry 1).

Table 5 Reaction optimization.



58 90

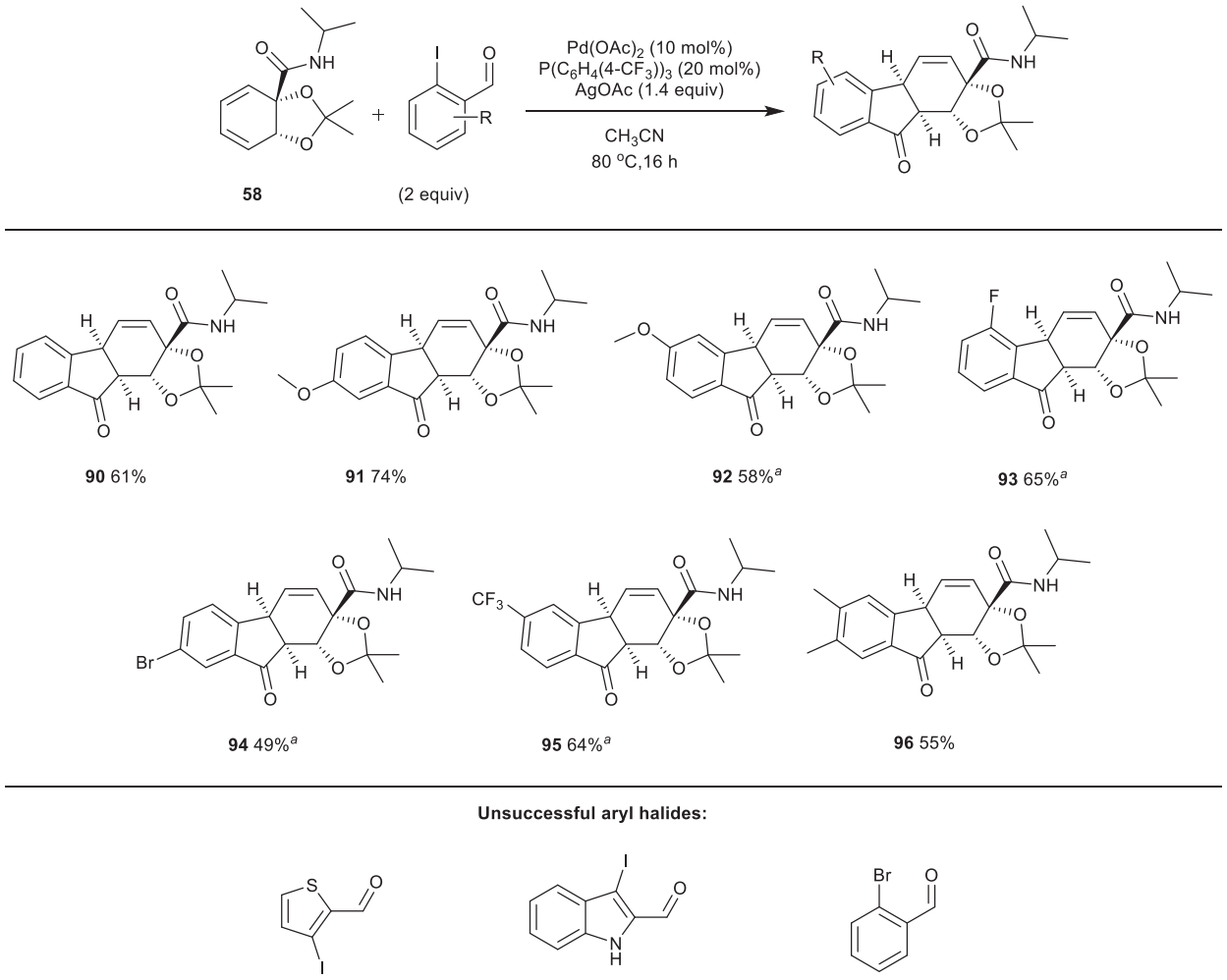
Entry	Catalyst	Ligand	Base	NMR yield %
1[a]	$Pd(OAc)_2$	$P((4\text{-}CF_3)C_6H_4)_3$	AgOAc	66
2	$Pd(OAc)_2$	PPh_3	AgOAc	6
3	$Pd(OAc)_2$	$P(4\text{-}F\text{-}C_6H_4)_3$	AgOAc	5
4	$Pd(OAc)_2$	tri(2-furyl)phosphine	AgOAc	41
5	$Pd(OAc)_2$	tri-*o*-tolylphosphine	AgOAc	2
6	$Pd(OAc)_2$	dppf	AgOAc	46
7	$Pd(OAc)_2$	$P(OPh)_3$	AgOAc	32
8	$Pd(OAc)_2$	-	AgOAc	47
9	-	$P((4\text{-}CF_3)C_6H_4)_3$	AgOAc	-
10	$Pd(OAc)_2$	$P((4\text{-}CF_3)C_6H_4)_3$	NaOAc	-
11	$Pd(TFA)_2$	$P((4\text{-}CF_3)C_6H_4)_3$	AgTFA	17
12	$Pd(OAc)_2$	$P((4\text{-}CF_3)C_6H_4)_3$	Ag_2CO_3	2
13	$Pd(OAc)_2$	$P((4\text{-}CF_3)C_6H_4)_3$	Ag_2O	1
14	$Pd(OAc)_2$	$P((4\text{-}CF_3)C_6H_4)_3$	AgOAc[b]	53
15	$Pd(OAc)_2$[c]	$P((4\text{-}CF_3)C_6H_4)_3$	AgOAc	10

[a]24 h reaction time. [b]1.2 equiv AgOAc, [c]5 mol % $Pd(OAc)_2$.

As in the previous arylation studies, tris(4-(trifluoromethyl)phenyl)phosphine proved to be the most effective ligand (entries 1-8), and other bases than silver acetate (entries 10-13) were less effective. The reaction required palladium to proceed at all (entry 9) and reducing the loading of palladium (entry 15) or silver (entry 14) gave incomplete conversion to the desired product.

5.2.2 Reaction scope and limitations

The aryl halide side scope of the palladium-catalyzed cyclization was evaluated using a selection of aromatic and heteroaromatic *ortho*-iodo aldehydes, the results can be found in Scheme 52.

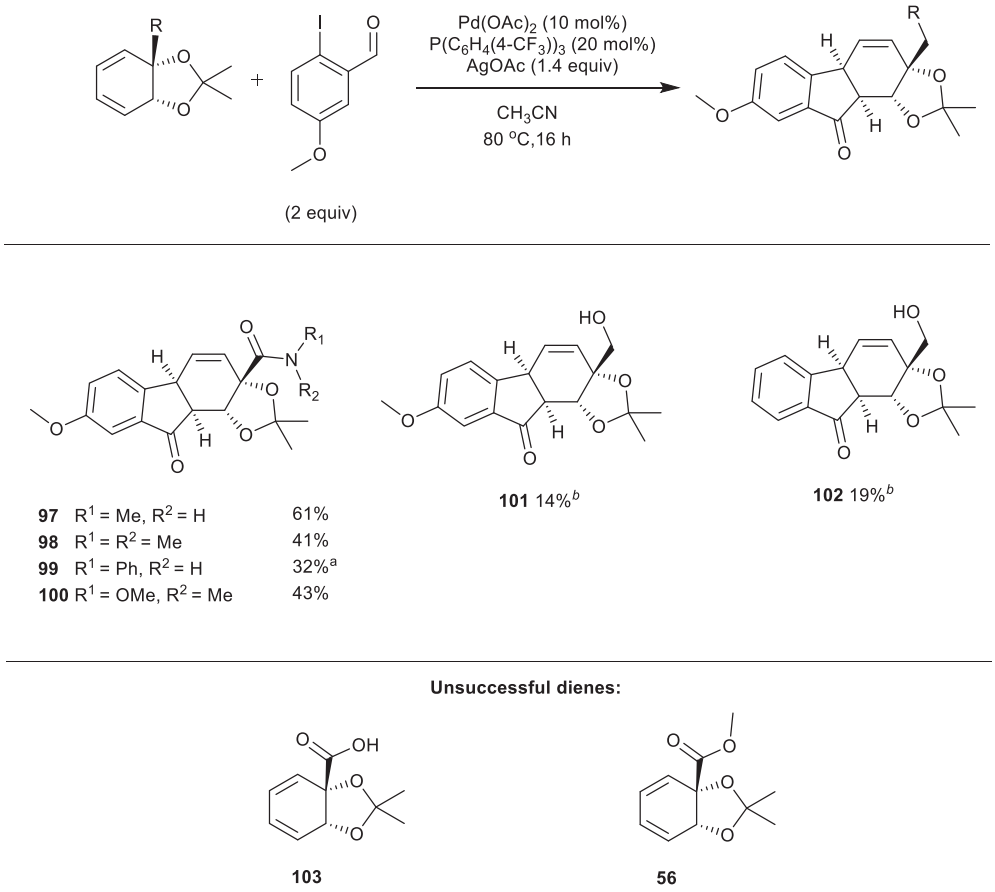


Scheme 52 Aryl halide scope and limitations. [a]100 °C in 1,4-dioxane.

Using unsubstituted 2-iodobenzaldehyde, the product **90** could be isolated in 61% yield. The reaction worked well for both electron rich and electron poor 2-iodobenzaldehydes and tolerated substituents in the *ortho, meta* and *para*-positions relative to the iodide. The highest yield of 74% was obtained using 4-methoxy-2-iodobenzaldehyde. When bromo-substituted 2-iodobenzaldehyde was used, the arylation was selective at the iodide position. Only trace amounts of **90** were formed when using 2-bromobenzaldehyde as the aryl coupling partner.

Two heteroaromatic aldehydes were evaluated but were unfortunately unsuccessful. Using 3-iodothiophene-2-carbaldehyde gave only traces of product, while 3-iodo-1-H-indole-2-carbaldehyde gave a complex mix of reaction products, where no desired cyclization product could be identified.

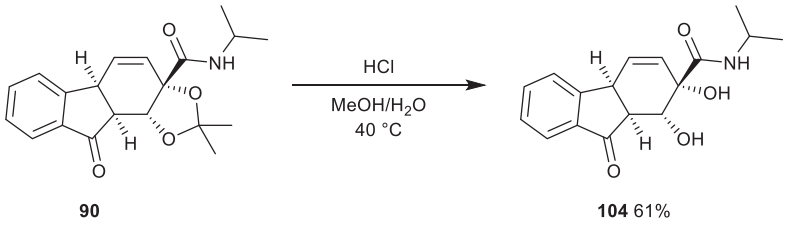
The scope was also investigated on the MAO-derived diene side (Scheme 53), where the carbonyl side chain was modified. The reaction tolerated both primary and secondary amides, a Weinreb amide was also compatible providing a useful handle for further transformations. A protected MAO-product with the carboxylic acid reduced to an alcohol could also be used as a substrate in the reaction, however in somewhat disappointing yields. The reaction with the alcohol gave a complex mixture of products when acetonitrile or dioxane was used as a solvent, using DMF at 100 °C instead gave a cleaner reaction.



Scheme 53 Diene scope and limitations. [a]100 °C in 1,4-dioxane, [b]100 °C in DMF.

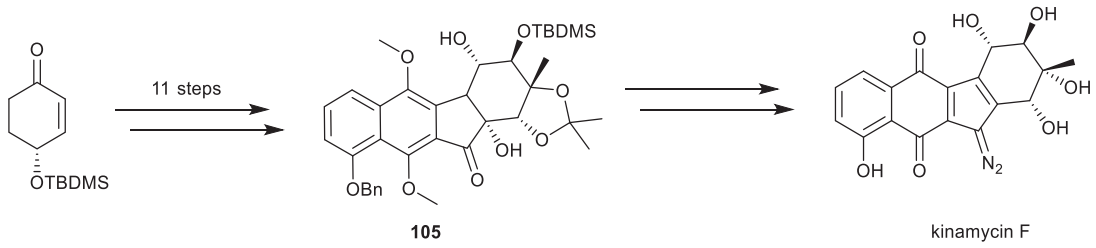
Acetal protected MAO-product **103** did not give any cyclization product under the tested conditions, instead resulting in degradation of the diene starting material. The methyl ester protected MAO-product **56** also failed to form any cyclization product, but in this case the starting material was intact at the end of the reaction.

The scope of products available from the palladium-catalyzed domino reaction could be further expanded to include the acetal deprotected free diol **104**, which could be isolated in 61% yield after treating cyclization product **90** with aqueous hydrochloric acid in methanol at 40 °C (Scheme 54).



*Scheme 54 Acetal deprotection of cyclization product **90**.*

The products formed in the palladium-catalyzed domino reaction represent a class of highly functionalized chiral tetrahydrofluorenones, a motif present in a several natural products with interesting bioactivity.[258,259] An example of similar molecules which has been the target of synthetic studies are the kinamycins, a class of tetrahydroflourenones showing antibiotic and anti-tumor activity. The first total synthesis of a kinamycin alkaloid was presented by Porco in 2006.[260] A total synthesis of kinamycin F, which was reported by Nicolaou in 2007[261] goes through an intermediate (**105**) structurally similar to our cyclization products. The intermediate was synthesized in 11 steps from a chiral enone (Scheme 55). As the kinamycins show interesting biological activity, these types of structures are of interest for total synthesis applications.

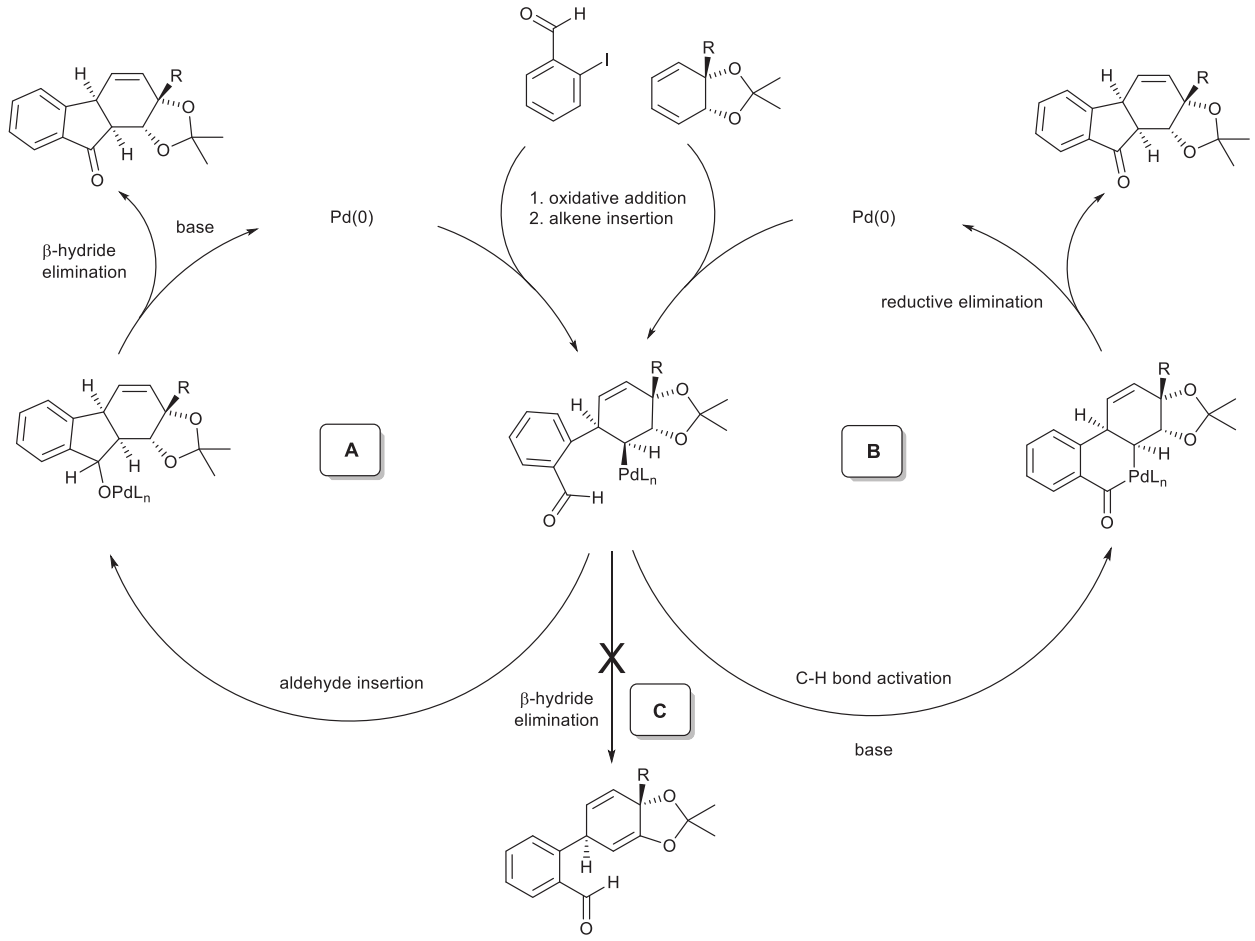


Scheme 55 Synthesis of kinamycin F.[261]

5.2.3 Mechanistic insight

In our previous arylation study, the reaction proceeded through a Heck-type mechanism terminated by a β-hydride elimination. In this project, we do not see any standard Heck-type product. However, the obtained cyclized products are consistent with an initial carbopalladation as in the previous study, but with termination by an intermolecular acylation rather than a β-hydride elimination (scheme 56, C). In the arylation project (paper III), the barrier for the corresponding β-hydride elimination was calculated to be 16 kcal/mol which is relatively high, potentially making acylation competitive.

Two different pathways can be proposed for the terminating acylation. It could be the result of an insertion of the aldehyde into the Pd-C bond, followed by an oxidation of the formed benzylic alkoxide by a β-hydride elimination (Scheme 56, A). Alternatively, the same product could be formed by a C-H activation of the aldehyde, followed by a reductive elimination to form the ketone (Scheme 56, B).



Scheme 56 Potential mechanistic pathways for the acylation step.

Only one other example of intermolecular acylation of an sp^3-carbon-palladium species has been described, where a *gem*-dichloroalkyl palladium species reacted with an aromatic aldehyde.[262] In this case, the authors proposed an aldehyde insertion type mechanism, although no mechanistic investigation was conducted. Several examples of intermolecular acylation of aryl palladium species have been reported, proceeding through both CH-activation[263,264] and aldehyde insertion[265–268] mechanisms. The reaction presented herein is, however, to our knowledge, the only example of an acylation-terminated Heck-type reaction.

No distinction can be made between the two pathways from our results, and they could prove challenging to distinguish between experimentally. Concomitant formation of the benzylic alcohol would be an indication of the aldehyde insertion pathway, formed when palladium is displaced from the alkoxide before it is oxidized by β-hydride elimination.[265,268,269] However, no unoxidized alcohol has been identified in our reaction. Kinetic isotope effect studies have been used to distinguish between these types of mechanisms in related reactions,[263,264] in our case however, the acylation is unlikely to be the rate limiting step. Efforts to shed more light on the mechanism of the acylation using DFT calculations are ongoing.

5.2.4 Summary and outlook

An unprecedented Heck-type carbopalladation-acylation domino reaction has been demonstrated. The interesting synergy between the biocatalytic transformations of benzoic acid and palladium-catalyzed Heck-type reactions is further expanded on, forming products of high structural complexity in just two non-trivial steps. The reaction uses a chiral starting material in the form of a protected MAO-product, together with an ortho iodobenzaldehyde, and utilizes the complexity present in the starting material, forming a tetrahydrofluorenone product while introducing two new chiral centers. The tetrahydroflourenone skeleton is present in several bioactive natural products, and we therefore envision that the developed reaction could be of interest for various synthetic applications.

Substitution on the aryl halide is tolerated, while none of the tested heteroaromatics was compatible. The reaction worked well with the carboxylate of the MAO-product converted to a range of different amides. When reduced to an alcohol, the reaction was still successful, although in low yields, while the free acid or a methyl ester did not afford the desired products.

The reaction most likely proceeds through a Heck-like catalytic cycle, with initial oxidative addition and carbopalladation, but is terminated by an intermolecular acylation rather than a β-hydride elimination. However, the mechanism of the acylation cannot be determined from our experimental results. As this acylation represents a novel type of termination in a Heck-type reaction, investigations to elucidate the mechanism would be of interest. Computational studies to gain further insight into the mechanism of this reaction step are underway.

6. Conclusion and outlook

In this thesis, two methods for the selective functionalization of bio-based molecules have been developed. The first method concerns nucleophilic addition to cationic iron carbonyl dienyl complexes. Here, the scope of the reaction has been expanded to include selective *C*- or *O*-addition of phenols, as well as the addition of azulene nucleophiles. Addition of phenols proceeded in good to excellent yields and could be directed with high selectivity towards *C*-addition by using ethanol as the solvent with no added base, or towards *O*-addition by using an aprotic solvent together with triethylamine as a base. The reactions were optimized to proceed under green conditions and were achieved in potentially renewably sourced solvents and with a base as the only additive in the case of *O*-addition. The *C*-addition of phenols could also be achieved in a more atom-economic manner. By using a neutral precursor to the cationic iron complex together with catalytic acid, the electrophilic cation could be formed in situ, removing one reaction step and reducing the amount of reagents and solvent used. Addition products of both phenol *C*-addition and azulenes could be demetallated to liberate the free diene, in both cases the diene could also be aromatized. Unfortunately, we were not able to access the demetallated phenol *O*-addition products, which would have further increased the utility of the reaction. A demetallated addition product of guaiazulene could also undergo a base-catalyzed cyclization, forming an interesting tetracyclic compound.

The second method uses palladium-catalyzed Heck-type reactions to derivatize products from microbial arene oxidation of benzoic acid. An interesting synergy between the microbial transformation and the Heck reaction allowed for a rapid introduction of molecular complexity. The palladium-catalyzed reaction gave good yields of arylated dienes, with complete regio- and diastereoselectivity despite the multitude of available reaction paths. This reactivity was also studied using DFT calculations, which was able to explain the observed selectivity. The optimal reaction conditions required a silver additive, which is not optimal from a green chemistry point of view. Attempts to optimize the reaction under silver free conditions were unfortunately unsuccessful in reaching sufficiently high yields. A domino reaction could be triggered by using a 2-iodobenzaldehyde as the aryl halide coupling partner. Instead of a Heck reaction terminated by β-hydride elimination, the carbopalladation was followed by an acylation between the formed organopalladium species and the aldehyde, forming a highly functionalized tetrahydrofluorenone. This type of reactivity is unprecedented following a Heck-type carbopalladation.

The developed reactions present new tools for the valorization of bio-based starting materials. Cationic iron carbonyl complexes can now be used for the selective alkylation of phenols, a class of molecules with abundant natural sources in the form of lignin. Functionalization of azulenes (including bio-derived guaiazulene) using this method could be of great interest as azulenes are promising in areas ranging from solar cells to colorimetric sensors. Spectroscopic investigations of the formed products suggest they could be interesting in for example multimodal sensing applications. The palladium-catalyzed arylations of MAO-products are able to introduce a high degree of complexity in just a few reaction steps from benzoic acid and the formed products could be useful for synthetic purposes. The developed palladium-catalyzed domino reaction demonstrates

a new type of reactivity, which could prove to be a valuable tool for synthetic chemistry, providing a convenient means to access complex tricyclic molecules.

Ongoing studies are focused on gaining insight into the mechanism of the terminating acylation of the palladium-catalyzed domino reaction using DFT calculations. As this is an unprecedented type of reactivity, elucidating the reaction path is of great interest. In the future, it would be desirable to incorporate the products of the MAO-product arylations in the total synthesis of bioactive compounds, for example in the preparation of kinamycin alkaloids. The addition reaction to cationic iron complexes could also be combined with the microbial arene oxidations, using iron complexes from MAO-products. Decomplexation of the phenol *O*-addition products would be interesting to explore further, where the mild photolytic conditions developed for demetallation of the azulene products could be a good approach.

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